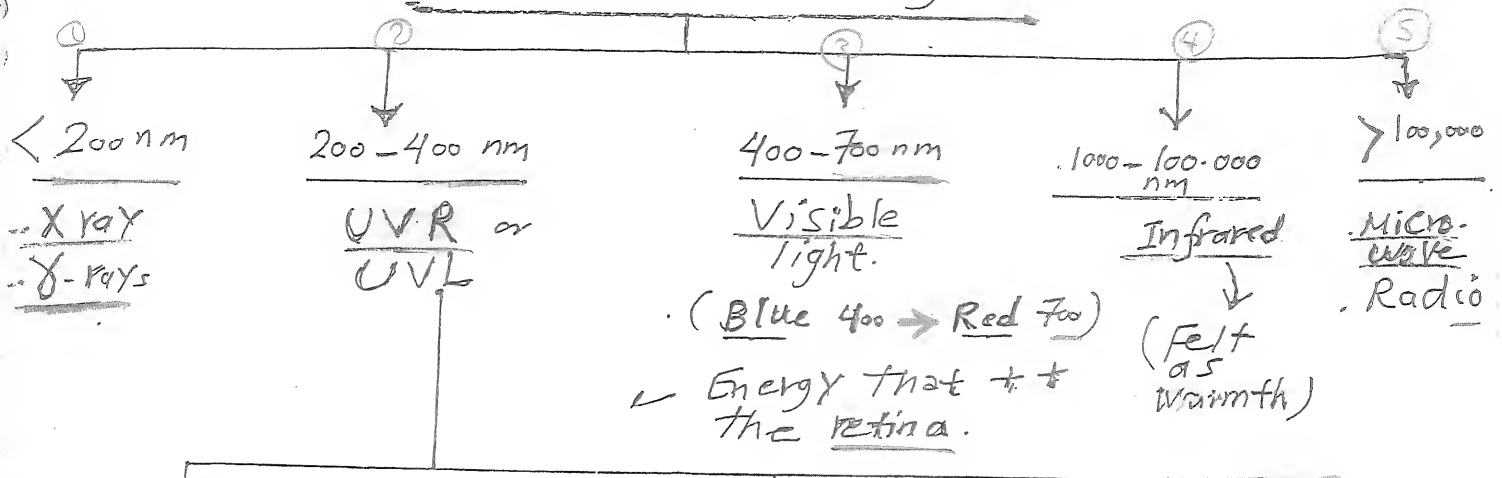
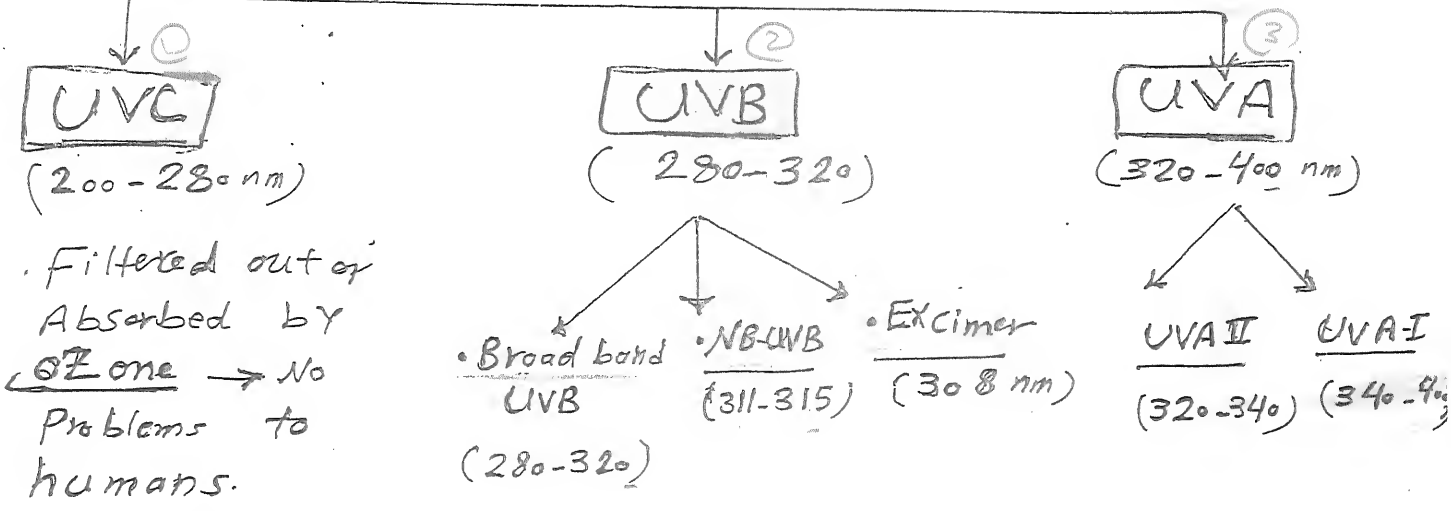
Light & Skin

(13) داعر كمير

Sun. Radiation spectrum According to the wave length:





UVA	UVB
. 320 – 400 nm	. 280 – 320 nm
. (5%) of UVRs (0.5% of spectrum) → طوال السنة وطوال اليوم بنفس الكمية	(95%) of UVR (6% of Rad. Spectrum).
. Greater in Amount (100 times > UVB) but 1000 times Less Potent (Erythemogenic)	. Maximum at (4th – 7th month of year, at (9 am – 4 pm).
. Penetrates deeply (Dermis & SCT)	. less in amount but more Erythemogenic.
	. doesn't penetrate the dermis (90% Absorbed by epid).

UVA	UVB
. Cut. effects:	
(1). Indirect DNA damage by releasing ROS → less carcinogenic	(1) Direct damage of DNA by Format of pyrimidine dimers
(2) Breaks Vit D ↓	(2) ++ Vit D synth.
(3) NO Epidermal Hyperplasia → No significant photoprotect	(3) ++ epid. Hyperplasia & Hyperkeratosis → Photoprotect (Hardening)
(4) Immuno modulat	(4) Immunomodulat.
"skin diseases"	
(1) Photoageing.	(1) Burn } epid.
(2) Photosensitivity (all diseases except CAD) UVB > UVA	(2) Cancer } epid.
(3) Darkening	(3) Tanning

• NB:

. Window glass blocks UVB only (<320)

. The more the skin hydrat → ↓te flexion & ↑ Absorpt → Burn.

. UVB is More Carcinogenic > UVA ?? → direct DNA damage; 90% of UVB Absorbed by epid. & Most Cut. Cancers are epidermal.

. Natural sunprotective Mechanisms:

1- epid. thickness
2. Natural Antioxidants
3- Melanin
4. Urocanic acid
5. DNA Repair Mechanisms.

Fitzpatrick Skin Types and Recommended Sunscreen Sun Protection Factor (SPF) Levels

Skin Type	Description	Skin Color	Routine SPF	SPF for Outdoor Activity
I	Burns easily, never tans	Very fair	15	25-30
II	Burns easily, tans lightly	Fair	12-15	25-30
III	Burns somewhat, tans readily	Olive	8-10	15
IV	Burns minimally, tans well	Light brown	6-8	15
V	Doesn't burn, tans deeply (Indians)	Dark Brown	6-8	15
VI	Rarely burns, always tans	Black	6-8	15

For this analysis, the global population was broken down into three broad skin pigmentationgroups, as there are insufficient data to separately quantify skin types I to IV:

1- Lightly pigmented – this includes skin types I to IV
2- Interme diate pigmentation – skin type V
3- Deeply pigmented – skin type VI

Cut Effects of UVR

1- Beneficial Effects → Vit. D synthesis. / Sense of well being.
2- Adverse Effects.

- Aging
- Burn
- Cancer
- Darkening & Taning.
- Photosensitivity

NB: Effects may be classified as: Acute / subacute / chronic

← Tt of Same skin dis. (Vitiligo & AD)

Effects

A - Acut:

1. Sunburn
2. Pigm & Darkening
3. Epid. Hyperplasia
4. Immunological

++ Immunity : ↑↑
- IL1, IL6, TNFα
- AMP.

-- Immunity
[↓ LCs
↓ Funct of LCs] عددها وظيفتها
[↑ IL10
↑ α MSH] Both -- Immunt
→ ++ Treg.

5. Repair
- NER
- Base ER
- Recombinat Repair
- Translesional DNA Synth.

B - Chronic

1- Aging

2 Types: Intrinsic: d.t Senescence (unpreventable) — الشيخوخة
Extrinsic: d.t UVR & Smoking (photoaging = Dermato-Heliosis).

TABLE 57-1 AGE-RELATED CHANGES IN THE SKIN

Intrinsic Aging	Extrinsic Aging (Primarily UV Light)
Decrease in corneocyte adhesion	Altered keratinocyte maturation (xerosis)
Slight decrease in epidermal thickness with flattening of rete pegs	Freckles (ephelides) = lentigo senilis = liver spot
Decreased number of eccrine sweat glands	Solar lentigo
Decreased numbers of hair follicles	Guttate hypomelanosis
Canities (gray hair)	Wrinkling
Thinning and ridging of nails	Elastosis (yellowish skin)
Decreased dermal collagen (decreases 1% per year)	Telangiectasia
Decreased number of dermal elastic fibers	Senile purpura
Decreased dermal ground substance	Venous lakes
Loss or increase in subcutaneous fat (site-dependent)	Comedones = favre Racouchet Synd.

- Solar < lentigo, Elastosis
- Senile < purpura, Comedones.
- dyspigm.
- Telangiect.
- Wrinkling, Xerosis
- Venous lake
- Comedones
- Colloid Milium
- Pseudoscars.
- Poikiloderma of Civatte ↓ vascular (sparing dorsal neck)

Laser

Some Manifs. of Aging

- dyspigm < Hyperpigm. (Hemosiderosis & purpura) / Hypopigm.
- Solar (Senile) Lentigenes (difference bet. freckles & Lentigenes)
- Some specific patterns:

1- Solar (Actinic) Elastosis: Yellowish Translucent papules & plaques on Neck & striated beaded lines (Sebaceous Hyperplasia).

2- Solar Elastomas & Elastatic Nodules of Ears: Yellowish papules Resemble BCC.

3- Senile (Actinic) purpura: dorsum of hand & forearm of Elderly → unresolved Hyperpigm.

(4.) Farmer's Neck (Cutis Rhomboidalis Nuchae)

(5) Favre-Racouchet synd:

- Elderly
- at Zygomatic bone & infra orbital
- 3 ⟨ cysts, Comedones, Elastosis.

(6.) Stellate pseudoscars: d2 lake of support of Bl. Vs d2 Collagen destruction

---

HL → Colloid Milium (كمعان) أصفرناصال (لاصة)

Condition ch. BY: Waxy ↗

① Multiple dome shapped Translucent, Amber flesh colored papules on sun exposed Areas.

② dermal Colloid Material on Mic. Exam.

Variants: [1- Adult onset. 2. Juvenile " [3- Nodular 4- Pigmented.

Pathophysiology ⟨ Et:- Source: -

. degenerative Condition linked to ③:

(i). Genetic (Inherited): Juvenile type
(ii). sun exposure
(iii). chemicals: petrolatum & (Hydroquinone) تفتيح

. origin of Colloid deposition in Dermis: unknown but ±

. degeneration of Elastic fibs in adult form. (or fibroblasts)

" " UV- Transformed KCs in Juvenile Form

. Cause: . Adult → Excess sun

. Juvenile → inherited suceptability to (UVR)

clinically

. lesion± ⟨ papular, Nodular, plaques Waxy, Translucent, Amber-yellow (Except in Pigmented type) أصفر

... expressed

- Lesions on Side of Face & Ipsilat. forearm → described in "Taxi Cab driver" "سائق التاكسي"

- Hydroquinone → pigmented Collard Milium sometimes in ass. ē ochronosis.

- Juvenile type ± ass. ē Ligneous Conjuctivitis or Periodontitis.

Histopath.
- similar to Amyloid in Histopath & Histochemistry but differs in EM
- Colloid material: intradermal, amorphous, Fissured, Eosinophilic material in dermis.
- to diff. bet. Juvenile & adult types
  - in it → apoptotic KCs over the Material
  - WL KCs

Ttt
1. dermabrasion, Cryo, diathermy, Lasers
2. VitC + Exfoliating agents.

Sunburn & Solar Erythema

Def. NL. cut. Reaction to sunlight in excess of an erythema dose = 4 SED on unacclimated White skin

Sunlight Exposure: . onset 6 hrs → Sunburn → 1w → desquamation.
. Peak 12-24 hrs (Peak level of NO)

Sunburn:
- Erythema
- Edema
- Tenderness
- ± blistering
- ± Constitutional manif. ← Fever, Chill, Hypotension

Usually d.t UVB. by direct VD or PG Mediated IL1 & iNOS → NO

Ttt
- once Redness & other Symptoms appear → Ttt become of limited Efficacy (as the inflamm. Cascade & damage is done)

PGE: is important mediators so:
- Aspirin
- NSAIDs e.g. Indomethacine
- Topical Cs & Soothing agents. (Betnovate & Calamine lot.)

Tan does not = irreversible pigm

• Pigment Darkening & Delayed tanning

- Darkening
- Tanning

after UVR exposure there are 2 Responses

- onset
- dur
- ↕
- Photoprotect.

* Pigment darkening (PD)

Immediate, Transient, "Grayish" Pigmentation that occurs immediately following exposure & Lasts for:

- 10-20 mins (immediate PD; IPD)
- upto 12 hrs (persistent PD; PPD)

* d.t: oxidation & Redistribution of Existing Melanin.

UVA: induced.

Not Photoprotective.

* Delayed Tanning

- Maximum ein (2) 2-3 ds & Lasts for (2) = 1-2 ws

* d.t: True Melanogenesis

* UVB induced:

* photoprotective against sunburn. (d.t Epid. Hyperplasia)

UVB ± UVA

- Immunosuppression: UVR exposure → ↓↓ CMI (↓ Alter LC activity, ↓↓ product. of suppressor TC, ↓↓ cytokines)
- Epid. Hyperplasia: UVR (UVB)(UVC) → Epid dermal st. Corneum → Hyperplasia → ± Photoprotective against sunburn

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• UVR & Cancer

- BCC
- SCC
- MM

Another Classification

سؤال إضافي

(A) Acute & Subacute Effects

- Burn
- Darkening
- Taning
- photosensitivity

- Immunosuppression
- Epid. Hyperplasia
- Vit D synth. (UVB)

- Others
  - Photomorphogenesis
  - mid-dermal elastolysis

(B) Chr. Effects

- Photoaging & Photocarcinogenesis

Cause of photosensitivity and photodermatoses

.all UVA > UVB
Except:
1- CAD
2. SLE.

Photosensitivity occurs for a variety of reasons. These can be classified into the following groups:

Photodermatoses	Causes
Idiopathic *(Probably immunologically mediated)*	Cause is unknown but exposure to UV light produces a clearly defined disease entity. These include:

- Polymorphic light eruption — PMLE
- Juvenile spring eruption
- Actinic prurigo
- Solar urticaria
- Chronic actinic dermatitis (Actinic reticuloid)
- Hydroa vacciniforme
- Pseudoporphyria
- Bracioradial Pruritus

(Actinic) 2 ← Solar urticaria, Pseudoporph.

Genetic

photosensitive dermatoses in children.

Photosensitivity is caused by a pre-existing genetic disorder, e.g.:

- Bloom syndrome
- Rothmund Thomson syndrome
- Cockayne syndrome — میکن ماوس
- Xeroderma pigmentosum
- Hartnup disease

PIBIOS

Metabolic

Photosensitivity is caused by a metabolic defect or imbalance of a body chemical. The most common disorders of this type are porphyrias , in which there are increased porphyrins in the skin. e.g. Porphyria

Exogenous (Drug-Induced Photosensitivity)

Photosensitivity is caused by the introduction of an external agent that is applied topically or administered internally. These agents are called photosensitisers (see Drug-Induced Photosensitivity) ..اتكلم عنها بالتفصيل

Photoexacerbated dermatoses

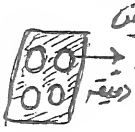
Photosensitivity is caused by a pre-existing disease or skin. These include conditions such as:

- Acne
- Atopic dermatitis AD
- Dermatomyositis DM
- Darier
- EM.
- GA
- Grovers disease
- Hailey-hailey
- LE
- LP
- Pellagra
- PRP
- Psoriasis, Pemphigus (Foliaceus), Rosacea, SD

NB: Although most people with the common skin conditions, psoriasis and atopic dermatitis (eczema) find sun exposure or ultraviolet light treatment helpful, about 10% report they cause flare-ups.

Lab Invs of photosensitivity:-

- HP
- ANA
- Anti Ro / Anti La
- porphyrins
- Phototest → Sunprotected & exposed areas
- Photopatch test
- infants & children → Urinary Amino acids.



→ Diagn. Solar Urticaria

سؤال امتحان

Polymorphous Light Eruption (PMLE)

Def: Acq. Idiopathic photodermatosis (Photodermatoses) — Commonest

- Pathophysiology → unknown but ∴ Immunologically Mediated by Type IV Hypersensitivity Reaction. in Response to UVL (UVA, B) [but UVA > UVB] [rarely visible]
- Epidimiology:
  - More in females : 2 : 1
  - More in skin types: I & II
  - (+ve) FH in : 10 - 50%
  - (+ve) ANA in 10-20% (photosensitive SLE may give history of PLE like eruptions for Ys. before SLE diagnosed.. so all cases of PMLE should be followed up for development of SLE).

Fem. + Hx +ve

- Clinically :-

Sun exposure

- onset: 1 - 4 days. (4hrs)
- Resolut: days.

→ Eruption (Polymorphic) — Papular / Papulo Vesicul. / Diffuse erythem. / Plaque (DD. DLE, Sens.) (pruritic)

- May have several Morphologies but in any 1 patient only one clinically form is consistently manifested.

- Papular (Commonest)
- Papulo Vesicular
- Eczematous
- plaque like (LE like ← Fixed Erythem. scaly)
- Pin point papular (Lichenitidus like)
- pruritus only (PLE sine Eruption.)

Later on → Eruption.

½ - several hs needed For development.

"lang" in amount of is more important than absolute amount.

in spring (rare in Winter) or early summer

appear in summer d.t phenom. of "skin Hardening"

start at onset of vacation in sunny places & ↓E

Return to home.

8. Juvenile spring Eruption.

9. Generalized (all ...

· Areas affected: usually sunexposed areas that's alway protected from UVL during winter months e.g Extensor forearms & Chest, While < Face / dorsal Hands → least affected (skin hardening)

الاماكن اللي كانت متغطية في الشتا

→ improvement ē summer & Autumn.

Juvenile Spring Eruption:

< Boy — papulovesic at Helices.

- child
- (ears)

· Age: Boys 5-12 (but ± Young Adults)

· Induced d.t exposure for sunny days during cold seasons.

التعرض للشمس فصل الشتا

· papules or papulo vesicles on helices.

· DD <
- L.E (more chr. ws-ms, Non-pruritic)
- photosensitive drug Eruption
- prurigo Nodularis.
- Solar Urticaria (more — < Whealing, Rapid onset, " Resolut, Recurrence) → تخف بسرعة

الأعم

· EPP (painful)

· Diagnosis:

(1) · Clinical → sufficient

(2) lab: <
- ANA → To exclude (SLE)
- Urinary & Stool porphyrins → to exclude (PCT)

(3) Provocative test: (phototest). exposure to UVA or UVB → lesion → Biopsy.

(4) HP: تحت
- Dermis: · patchy dermal infilt. < Interstitial / Periappendag / perivascular
  · upper papillary dermal Edema ± Neut.
- فوق · Epid. spongiosis.

٣ حاجات في LE
١- مصرح ظهوره مع الـ ...
٢- مكانه
٣- علاجه الضد

• Treatment :-

1- Sunprotect^ Program : يكتب بالطلب

2- Medications

· Topical : Cs

· Systemic : Cs, Antihistamines & AZathioprin. or Antimalarial.

3- Phototherapy : prophylactic during (Spring) to produce skin hardening. (to maintain Hardening) أسابيع وبعدها يعود تعرض للشمس بالربيع بداية ٥ أسابيع - بداية الربيع

(± Cs)

→ · UVA or UVB

· systemic Cs : (±) Needed to prevent Eruption during phototherapy. أدوية قبل وأعراضها ٣ مرات أو مرتين لمدة ٥ أسابيع

Actinic Prurigo

(Hutchinson's summer prurigo)

· May be Variant of PMLE ; AET. may be:

① photosensitive disorder to UVA & UVB
② Immunologically mediated Genetic dis.
③ Persistent Variant of PLE

* · Age: → more common in children. (قبل 10 yrs) (F > M)

* · clinically : (1) Severely pruritic: (AD or Acute PLE like)
- papules
- Nodules
- papulovesicles

(2) Eczematizat^
· Hyic Crustat^ → (3) linear & Pitted flat scars & dyspigm.
· Lichenificat^

(4) Ass c: 4 (عكس) Conjunctivitis & cheilitis . Pseudomadarosis (d.t

- Site : sun exposed then → sun protected areas.
- Course: . Chronic, persistent throught childhood, but often fade in Adolescence.
  . Persistent throughout (Year) ē exacerbat in Spring & Summer.
- HP: . Acanthosis
  . Spongiosis
  . Dermal Edema
  . Lichenificat
- DD: Nodular prurigo, Photosensitive AD, EPP, Scabies, PMLE / photo CD
- HH 1- as PMLE
  2- Thalidomide showed to be effective.
  3- Cyclosporine (if ... not effective).

Brachio Radial pruritus

(Solar pruritus) (Nerve Trauma + UVL → Mid outer arm.)

- Condition in ẅ thereis: Itching + burning + Change in sensato + Lichenificat (Late), Hyperpigm., Bruises.
  . Affect one or both arms sp. The outer aspect of Mid-arm.
- AEt: Nerve damage. d.t Cervical spine dis. that's shows ↑↑ ē sunlight Exposure. (Light: Eliciting factor; Spine dis: predisposing factor)
- HH → Neurological assesmat for (Cervical Rib, T in, osteoarthritis)
  → Sunscreen.
  → Capsiacin, Local Anaesthetic
  → Amitriptyline. (أميتريبتيلين)

Hydroa Vacciniform

(updated DNNZ & Emed 2014)

(Vesicle) (Vaccinia like scar)

- **Def.** Rare photosensitive (UVA) dermatosis ch.BY by Recurrent attack of: (after 6 hrs)
  1. Hydroa: Fluid filled blister. (Maculopapular → painful pruritic Hgic blisters)
  2. Vacciniform scar: small pox like scar.

- **Age** . 2 ♀ > ♂
  - Childhood 2 peak → 1-7 Ys, 12-16 Ys → Resolve at 20 Ys.
  - Adulthood (rare)

- Some cases ass. ē (EBV) ch.BY: (CH. Vacciniform like lesions)
  1. Severe wide spread (sunprotected)
  2. Systemic S & S (fever, HSM, EBV by PCR)
  3. ↑ Incid of leuk. or lymphoma

(Margin box:) ناس .لو جيت تتكلم عنها ٣ كلمات
1- child (3-15), ♀
2- Blister erupt̄
3- Vacciniform scar → تختفي 20 Ys
4- DD
5- ?? Lymphoma

- **DD**: Erythropoietic protoporphyria (EPP)
  - disturbed porphyrin level.
  - Burning ē mins. of exposure.
  - Wax like scarring (Not Varioliform).

(Margin box:) Path. E/4: epid. degen. & Dermis: infilt, & thrombosis → Necrosis ? Both.

- **Tt**.
  1. Photoprotection.
  2. Anti malarial
  3. Antioxidants
  4. Phototherapy (desensitizat).
  5. Tt of EBV
  6. Stem cell Transplant (if lymphoma).

- **NB** Hydroa Aestivale → Mallorca Acne also is childhood vesiculo-papular photoeruption of unknown AEt. but differ from H. Vacciniform in "No scarring"

Chronic Actinic Dermatitis: (UVB)

def. photosensitive disorder that represent the end stage of progressive photosensitivity.

- Old names: . persistent light Reactivity.
  . Actinic Reticuloid (Resemble: Reticulosis or cut Lymphoma on Biopsy).

- clinically - usually Elderly >50 ys. ē occupational sun-exposure (farmers).

- Early → Lichenoid . Late → Pseudolymphomatoid (So Called Reticuloid)

Scaly
Early - Severely itchy Excoriated Papules & Plaques later →
Pseudolymphomatous papules & plaques

- there may be:
  - Nodules → Leonine face ē deep furrows
  - Generalized affection → Erythroderma & Generalized L.N
  - dyspigm. (Vitiligo like).
  - diffuse alopecia d.t severe Prolonged rubbing

يوصل للانتحار → . Severe Itching → ± suicide

AEt. unknown but ± Preceded by ECZema:-

- AD
- ACD
- Photocontact Dermatitis → UVB mainly.
  → Allergens as (Compositae plants, Rubber, Fragrance)

Course: life long; but some cases may show spont. Resolut^
: 10% → 5 ys
: 20% → 10 ys

CAD

1. UVB
2. HP:
   - MF
   - Band-like infilt. of Histiocytes & Lymphocytes .. ± invade epid. "Pautrier Microabscess"
   - Cells → Nucleus: Like MF Cells
     ↓ Mitotic figure.
3. CAD like CTCL → HP. Immunohist. TCR. will differentiate

Hyperkeratosis
Spongiosis
Dermal infilt (H+L)
MF Cells

Q .. DD Leonine Face:

- Leprosy
- Leishmania
- Lymphoma (T & B Cell).
- Leukemia
- Mastocytosis (Nodular)
- Sarcoidosis
- Amyloidosis (systemic)
- Proteinosis.
- Histiocytosis
- Scleromyxedema (Mucinosis)

chemical & Drug-Induced Photosensitivity

Def: development of cutaneous disease as a result of the combined effects of a chemical and light. Exposure to either the chemical or the light alone is not sufficient to induce the disease; however, when photoactivation of the chemical occurs, one or more cutaneous manifestations may arise.

Types (A) Phototoxic: subtypes
- Phytophotodermatitis
- Pseudo-PCT
- Lichenoid DE

(B) Photoallergic:-
- SCLE
- Photo-onycholysis
- Slate-gray pigm.

Aetiology: Photosensitivity reactions may result from topical or systemic medications + exposure to the UV-A_1 (320-400 nm) (also visible light may induce). Most *phototoxic reactions* result from the systemic administration of drugs while *Photoallergic reactions* can be caused by either topical or systemic administration of the chemical. There are some Compounds that commonly cause both reactions.

it is often difficult to differentiate phototoxic from photoallergic reactions. However, they have a number of distinguishing characteristics (see Table below).

Feature	Phototoxic Reaction	Photoallergic Reaction
Incidence	High ↑	Low ↓
Amount of agent required for photosensitivity (Allergen)	Large ↑	Small ↓
Type ↑ Agent (Drugs) Frequency of exposures	usually (Systemic > Topical) One صرة أولى مرة	(Topical > Systemic) More than one
Onset of reaction after exposure to agent and light	Minutes to hours	24-72 hours (1-3 d) ← Previous Sensitization
Distribution	Sun-exposed skin only "Burning or stinging"	Sun-exposed skin, may spread to unexposed areas (e.g. dorsal hands, V area of chest)
-Clinical characteristics -Hyperpigmentation	Sun burn like ± (Past) inflamm. Hyperpigm.	Eczema like; (NO) PIH (itchy) → Sites: - Periorbital - Submental - upper eyelid
Mechanism	direct damage to tissue caused by a photoactivated compound (except PUVA)	Type IV hypersensitivity

NB : Other less common skin manifestations of phototoxicity include pigmentary changes. A blue-gray pigmentation (With or without past history of burn like eruption) is associated with several agents, including

Incid. Mechan. Agent ← Type. amount frequency of exposure
Clp ← onset. lesion. site. past

- Example of Photosensitizers:

  - Tetracyclines
  - Quinolones
  - Naproxene
  - Isotretinoin
  - Antimalarial
  - Dapsone
  - Thiazides

  - Topical
    - Sunscreens
    - 5FU
    - Coal Tar.

Investigations: (قراءة عناوين)

1. Assess urine porphyrin levels (to diff. between pseudo-porphyria and porphyria cutanea tarda), ANA and anti-Ro (SS-A)

2. Photopatch testing is an important tool in the diagnosis of photoallergic contact dermatitis.
   ↳ drug + Sun exposure of skin

3. Histologic Findings

- *In acute phototoxic reactions*
  - Spongiosis
  - KC. Necrosis (Sun burn cells)
  - Mixed dermal Infilt.
  - if Pigm. is present its either d/t → Melanophages or deposits of metabolites in dermis

- Photoallergic reactions : as ACD (Spongiosis + mixed dermal Infilt.) but presence of KCs Necrosis suggest Photoallergy.

Treatment

1- The main goal of treatment is to identify the photosensitising agent and if possible to avoid it. In cases where medication is being taken to treat an existing condition and can not be discontinued, patients should be advised to follow sun protection strategies, including wearing sun protective clothing and using sunscreen.
2- Topical corticosteroids

photo test → light + skin

هاني أبو الوفا
مدرس الجلدية والتناسلية والذكورة
م. بكلية الطب

Sunscreens

صرية / حرارية / كيميائية

Systemic

Block Both UVA & UVB

→ Antimalarials

only UVB Blockers

→ Antioxidants (± used < Topical or Systemic)

- Vit. C (1gm/d)
- Vit. E (400 IU/d)
- Caratenoids eg β Carotene < Adult: 60-180 mg/d; child: 30-90 mg/d given to maintain (level 600 ug/dl)
- Green tea
- Poly Podium Leucotomas
- others: NSAIDS, selenium.

علشان لو ج أي مرض متعلق بالشمس اكتب Antioxidant.

⊙ Mechanism of photoprotective action of Antioxidants

1. Scavenging free radicals & Ros
2. ↓ No of UV induced sunburn cells
3. Preserving LCs.

Topical

⊙ Physical Sunscreens (sunblock)

- Inorganic, Inert,
- Large sized particles
- So < No CD. / Cosmetically bad
- Block both UVA & UVB (all wave lenghts: B, A, Visible)

⊙ Mechanism: Light Reflexion & scattering

as: . Zinc oxide (®) غالية
. Titanium dioxide
. Kaoline

→ . A1 cream
. Zincosil cr
. ultracare cr.

⊙ Chemical Sunscreens

. See the table

- Organic, Small sized So: -
- ± < CD / Cosmetically Accepted
- Mainly effective c̄ UVB & ± UVA

⊙ Mechanism:
Light absorption → harmful Energy is Converted to non harmful one.

Chemical absorbers

The table below is a list of some of the common chemical absorbers available and the protection they provide against the UV range.

Chemical	UVB (290-320nm)	UVA II (320-340nm)	UVA I (340-400nm)
Aminobenzoic acid derivatives			
PABA	Partial	None	None
Glyceryl PABA	Partial	None	None
Padimate O	Partial	None	None
Roxadimate	Complete	Partial	None
Benzophenones			
Dioxybenzone	Complete	Complete	Partial
Oxybenzone	Complete	Complete	Partial
Sulisonbenzone	Complete	Complete	Partial
-Cinnamates			
Octocrylene	Complete	Complete	Partial
Octyl methoxycinnamate	Complete	None	None
Salicylates			
Homosalate	Partial	None	None
Ethylhexyl salicylate	Complete	None	None
Trolamine salicylate	Complete	None	None

*Chemical absorbing sunscreens often contain a combination of ingredients to get coverage against both UVB and UVA radiation. Some are also combined with physical blockers.

* PABA should be avoided in children younger than 6 months because it can cause skin irritation.

* *Efficient* (Benzophenones, Octocrylene), *less efficient* (PABA and Salicylates).

other groups

- Avobenzone, Ecamsule } No UVB, Block of UVA I/II
- Bimotrizinol (Tinosorb) all

NB. Most sunscreens contain both physical ✓ & chemical preparations.

(HL)

- Polypodium Leucotomos
  - plant extract that has antioxidant effect & DNA protective effects
  - used in combination with green tea extract & beta-carotene in NewZeland under the name of (Heliocare®)

- Some defintions of sunscreens:

① - SPF: $\frac{\text{MEDs Protected by } 2mg/cm^2 \text{ of sunscreen}}{\text{MEDs unprotected}}$

What dose it mean that: SPF 15; this means that this sun screen provides 15 times protection (from UVL) when applied than when not applied

or if ē unprotection; MEDs occur after 10 minutes this sunscreen prevent MED for upto 150 mins.

$\left(\frac{150}{10} = 15\right)$

- the higher the SPF the better of skin protection & also compensate for underapplication.

- SPF of
  - 10 —Protect→ 90%
  - 15 ——→ 93%
  - 30 ——→ 97%

] → التأثيرين متقاربين لذا فالاهم ليس ↑SPF ولكن في الاستعمال الصحيح

- SPF ≥ 30, Expressed as (SPF 30+)

ومفيش حاجة اسمها > 30 (Above 50 = 50+)

- SPF = (sun protection factor) —FDA 2007 changel Name→ Sunburn Protection Factor.

طلعت ١/ سؤال

② - Sunscreen substantivity: the ability of the product to maintain its efficacy under the stress of prolonged excercise, sweating & swimming; whatever Repeat application several times
- → during exposures
- → After swimming & sweating.

سؤال

③ • Water Resistant : SPF maintained for 40 mins after Immersion.

④ • Water proof : SPF maintained for 80 mins after Immersion.

تغيرت FDA 2007 ↓ Very Water Resistant

Whatever, some authors don't agree with those Resistant & proof & recommended application After swimming & sweating.

NB • Most sunscreens (chemicals) effective ∈ shorter wavelengths (290-320) but Benzophenones provide more UVA protection. (against UVA1).

② Physical sunscreen may absorb (some) UVL → Free Radicals so some products contain Silicon Coat For Absorbtion of these free Radicals.

---

* Sun protection doesn't Means use of sunscreen only but equals = Sun protection Program

1- Avoid mid-day sun (10 am - 4 pm)
2- Seek shade.
3- Wear protective clothes/hats, Sunglasses
4- use sunscreens (Topical < physical / chemical + Antioxidant) → systemic

Def. clothing thats made of UV protective fabrics

protective fabrics: these are fabrics that achieve a minimum UV protection Factor (UPF also SPF) of at least UPF 15 after the equivalent of 2 yrs of NL Wear & tear.

UV protective clothes ch. BY

بوليستر
1- 100% Polyester (contain benzene ring that absorb UVL)

غامقة
2- dark clothing (dye absorb UVL 5 times > white)

مسام ضيقة
3. tightly woven fabrics مسامه ضيقه

طويلة
4- Long — sleeves
— pants سروال - بنطال
شنورة — skirts & shirts
— Collars & high Neck lines.

واسع وطبقات
5- Loose clothing. (Folds of loose clothing → double fabrics sun protection).

ملابس ناشفه بعد البسه
6- Coverup with dry clothes after swimming or getting wet.

اغسلها بأيه ؟!
7- Wash ē detergents that contain optical Fluorscent brightness. (act like dyes absorb UVL).

برنيطه
8- Hats with (4 inch) brim all around.

نظارة
9- sunglasses Blocking UVA & UVB

UV Index

1- بلاش خروج من (١٠-٤م)
2- إمشي ف الضل
3- الملابس — بوليستر / غامقة / واسعة / طويلة
4- نضارة شمس
5- برنيطة
6- شمسية
7- Topical sunscreen + Antioxidant

→ For Any Patient ē photosensitivity

22
17

How to use sunscreens ?

To get the best protection from your sunscreen you should consider the following points:

- Use a good broad-spectrum sunscreen of at least SPF 15 and made up of a benzophenone chemical absorber plus a physical blocker (titanium dioxide or zinc oxide).
- Apply sunscreen liberally to all sun-exposed areas so that it forms a film when initially applied. Most people use sunscreens improperly by not applying enough.
- Dual application technique : It takes 30 minutes for sunscreen to be absorbed by the skin and it can be rubbed off very easily, so apply it at least half an hour before going out in the sun. Reapply after half an hour after exposure (imagine you are painting a wall – two coats of paint provide a more even cover than one). This *dual application technique* is designed because the most common cause of sunscreen failure is under application (many studies showed that most users apply 25% -75% of standard amount , so SPF is much reduced).

NB: *The standard amount is that:* one teaspoon should cover the face, each arm, each leg and exposed parts of neck and shoulders. Two teaspoons can cover the entire torso.

- Re-apply sunscreen every 2 hours if staying out in the sun .
- Re-apply immediately after swimming, excessive sweating, or if rubbed off by clothing or towelling. This should be the case even if the product claims to be "water resistant" (Activities such as sweating and swimming degrade its effectiveness. The FDA is banning what it calls misleading labeling on sunscreens such as the use of the words *sunblock, waterproof,* and *all day protection* will no longer be used)
- Insect repellents reduce the sunscreen's SPF so when using together, use a sunscreen with a higher SPF and re-apply more often.
- *Which sunscreen, if any, should I use?*

**Alcohol-based lotions*, sprays or gels are better for oily or hairy skin, *Creams* are suitable for dry skin, and *milky lotions* are the easiest to apply. Special sticks are suitable for noses, lips and around the eyes.

25

18 23

What about Vitamin D?

If you have fair skin you may need only 5 minutes of midday summer sun activity in shorts and t-shirt without sunscreen to make enough. You will need longer or greater skin exposure if your skin is darker. Being physically active outdoors helps you make more Vitamin D than resting in the sun. If you are over 50 years old (ageing skin is not as good at making Vitamin D), immunosuppressed or have had previous skin cancers, you are better to apply sunscreen and talk to your doctor about Vitamin D supplements.

Sunscreen applied to babies (below 6 months) on limited areas. Vitamine D supplementation may be recommended with the most stringent sunprotection practices (some authors didn't recommend sunscreen for children beow 9 months but other sun protection programs should be carried out).

- Male sexual dysf. ??

26

Bologna
Erred
Comment
Dermati
± Arthma
دلالسي

سؤال امتحان

Erythemas

def. change in color of skin d.t dilatation of BVs specially Those of papillary & reticular dermis. As arteries & Veins may be involved; the color can vary from pink (art) to dark red (A+V) to Violaceous (venous)

أعراض

التسمية
د/ دارزني
برلرشيا

Types : A- Diffuse:

shape على حسب

Morbilliform = Maculo papular
1. Viral < Measles, G. Measles, Roseola
2. IMN Treated ē penicillin.
3. Drugs.

Scarlatiniform
- Scarlet fever
- Kawasaki
- SSSS
- TSS
- Septicemias
- Drugs

Roseolar = PR
- Pit. Rosea
- Drugs
- S.

B- localized:
- Trauma
- Heat → Erythema Ab Igne.
- Chemicals irritants.
- physical irritants e.g < Cold, Light
- Drugs.

C- Palmar Erythema: ~~DD~~
- pregnancy
- Thyrotoxicosis
- SLE
- RA
- LCF ← Liver Cell failure
- familial
- Computer.

Q Computer induced skin dse?

سؤال امتحان (D) Annular (Figurate) Erythemas: See below — Gyrate

(E) other Types:

سؤال 1. Flagellate Erythema: (Linear streaks)

- Chemotherapy sp → Bleomycin, docetaxel
- Dermatomyositis
- Adult onset Still's dis.
- Shiitake Mushroom dermatitis

2. Reticulated: Cut. PAN. & EAI

Erythema ab igne

3. Intermittent: Flushing ✓ سؤال امتحان

NB: Most Erythemas last for days → Months but some last only for minutes (Flushing).

Erythema ab igne (EAI)

(Toasted skin syndrome, Fire stains) (Laptop thighs / hot water Bottle rash) .

Def: localized areas of reticulated erythema and hyperpigmentation due to chronic and repeated exposure to infrared radiation heat at a lower level than that which causes a thermal burn.

Pathophysiology: repeated heat exposure in the range of 43-47°C that induces injury to the epidermis and superficial vascular plexus. Histopathologic changes similar to those seen in solar-damaged skin.

- Although the pathogenic mechanisms in erythema ab igne are poorly understood, one study has shown that moderate heat acts synergistically with ultraviolet radiation to denature DNA in squamous cells in vitro.

→ The following is a summary of heat sources reported to cause EAI: Heating pads. Hot water bottles (For pain relief in cancer pancreas and myositis). Electric stoves/heater, Open fires, Coal stoves, Peat fires, Wood stoves. Steam radiators.
- Car heaters, Heated reclining chairs, Heating or electric blanket, Hot bricks,
↳ Infrared lamps, Microwave popcorn, Laptop computer, Automobile seat heater, Hot bathing

Epidemiology: more in middle aged obese women.

C/P: Transient, blanchable reticulated erythema → persistent erythema → reticulated hyperpigmentation → development of: AK, SCC, Merkel cell carcinoma

- **Typically, erythema ab igne affects the legs of women aged 40-70 years who use indoor fire as a heat source. Erythema ab igne reportedly affects the face and/or palms of cooks who work over an open fire. EAI of the abdomen, flank or mid-back may reflect an attempt to relieve pain from inflammation (e.g. pancreatitis, peptic ulcer disease) or malignancy (e.g. pancreatic, gastric).** Other sites are according to heat exposure

- Other clinical variants of erythema ab igne are as follows:

1 - Bullous EAI (associated with normochromic normocytic anemia and subclinical hypothyroidism)
2 - Hypertrophic or hyperkeratotic and Keloidal EAI (associated with lymphedema)
3 - Poikilodermatous EAI

Pathology: epidermal and dermal atrophy, abnormal elastic fibers, capillary vasodilation and dermal pigmentation (both melanin and hemosiderin). Focal hyperkeratosis and dyskeratosis are noted along with squamous atypia.

Differential diagnosis: EAI needs to be distinguished from livedo reticularis, which is a temperature-sensitive vasculopathy that favors the extremities but only occasionally develops associated hyperpigmentation. The presence of telangiectasias along with atrophy and hyperpigmentation raises the possibility of poikiloderma and its various causes. MF , dermatomyositis .

Figurate (annular, gyrate) Erythemas

Figurate erythemas are characterized by lesions that are annular, arciform or polycyclic in configuration. Although a wide range of cutaneous diseases can have an annular appearance , there are four 'classic' figurate erythemas:

1-Erythema annulare centrifugum
2-Erythema marginatum
3-Erythema gyratum repens
4-Erythema migrans
5-Annular erythema of infacncy
6- Annular erythema associated with extractable nuclear antigens

بولونيا ذكر اول ٤ لكن Rook اضاف النوعين ٥و٦.

Erythema Annulare Centrifugum (EAC)

- **Etiology & Pathophysiology:**

EAC usually (Idiopathic) but it may be d.t Hypersensitivity reaction to variety of Agents including:

1- **Infection:**
   - Bact. → E Coli & strept.
   - Viral → EBV, Molluscum, HZ & HIV
   - Fungal → Dermatophytes & yeast (sp- candida).
   - Parasitic → ascaris & pthirus pubis.

("Woolf's Isotopic phenomena.)

2- **Drugs:** specially
   - NSAIDS ✓
   - Gold
   - diuretics ✓
   - Antimalarial
   - piroxicam
   - penicillin ✓
   - Aldactone.

3. **MG:**
   - Leukemia
   - Lymphoma
   - Cut-Tms (SCC)

4 **others:**
   - Food (Tomatoes)
   - stress, Menses, pregnancy
   - Sarcoidosis, SS, CA

- **Epidemiology:** .Age: → any, but peak usually at (50 ys).

.Sex: → No predilection .Race → No predilect-

.NB AD inheritance reported «Familial EAC»

I/P .the lesions start as Erythematous papules that spread Peripherally while clearing Centrally & Enlarges at arate of (2-5 mm/d) → Annular, Arciform, Figurate or Poly-Cyclic (festooned) plaques or patches.

دايرة بتوسع

.There are 2 clinical varieties:

A **Superficial Type:-**
   - Scaly → desquamat- at inner Margin «Trailing Scales».
   - Pruritic
   - non indurated or infiltrated.

Erythema Annulare Centrifugum (EAC)

Etiology & Pathophysiology:

EAC usually (Idiopathic) but it may be d/t Hypersensitivity reaction to variety of Agents including:

1- Infection:
- Bact. → E coli & strept.
- viral → EBV, Molluscum, HZ & HIV
- Fungal → Dermatophytes & yeast (sp- candida).
- parasitic → ascaris & phthirus pubis.

("Wolff's Isotopic phenomena")

2- Drugs: specially
- NSAIDS ✓
- Gold
- diuretics ✓
- Antimalarial
- piroxicam
- penicillin
- Aldactone.

3. Mg:
- Leukemia
- Lymphoma
- Cut-Tms (SCC)

4 others:
- Food (Tomatoes)
- Stress, Menses, pregnancy
- Sarcoidosis, SS, CA

Epidemiology:
- Age: → any, but peak usually at (50 ys).
- Sex: → No predilection
- Race → No predilect-
- NB AD inheritance reported «Familial EAC»

IP
- the lesions start as Erythematous papules that spread Peripherally while clearing Centrally & Enlarges at arate of (2-5 mm/d) → Annular, Arciform, Figurate or Poly-Cyclic (festooned) plaques or patches.

دايرين بتوسع

- there are 2 clinical varieties:

A Superficial Type:-
- Scaly: → desquamat- at inner Margin «Trailing Scales».
- Pruritic
- non indurated or infiltrated.

B deep Type EAC:

- Non scaly
- Non pruritic
- Indurated ⟶ = deep

- **distribution of lesion:** usually thighs & legs but may affect UL, Trunk & Face with sparing of palms & soles. xx

- **Course:** ⟶ Ws - ms
  - Exacerbation & remission may occur (with flare or recurrence of Et.)
  - ⟶ No residual scarring but ±: post-hyperpigm. or purpura.

⟹ **NB** White banding of Toenails reported in ass. with EAC.

Histopathology

- **Superficial EAC** (non specific)
  - Epidermal changes
    - Mild spongiosis & parakeratosis (so lesions are scaly & pruritic)
  - Dermal changes
    - ✓ Mild, superficial (upper dermal)
    - ✓ كُم Coat sleeve lymphohistiocytic infilt. (so Border of lesion less indurated).
- **deep EAC** (Classical Type) (more specific)
  - Epidermal changes
    - ↓ NO (so no scales / pruritus)
  - Dermal changes
    - ✓ dense, deep (mid & lower dermal)
    - Coat sleeve Lymphohistiocytic infilt.

أهم حاجة في الباثولوجي: Coat (غلاف) Sleeve (كُم) infilt. = infilt. is tightly cuffed around the BVs.

Treatment (Non Specific):

1- ## of underlying possible Etiology e.g Dermatophytosis.

2. Symptomatic ## e.g Antihistamines.

3. Topical Cs to the active border (beneficial)

4. Some authors → Empirical antibiotics & antifungal (Itraconazole or Terbinafine) → Cipro or Azithro.

5. Systemic Cs → remission may occur but recurrence is common.

6. Case reports:

- Metronidazole ✓
- Calcineurine inhibitors (CIs)
- Calcipotriol
- IFN-α → dramatic ē Infantile EAC
- Etanercept
- intraarticular Hyalutonic acid.
- EAC + Hyper Eosinophilic synd → Dapsone / Ketoconazole / septrin.

Exhausted Workup for Mg Not indicated as the rebate but EAC & it is not consistent

مفيش علاقة لابتة Mg ج

HL

X

Wolf's isotopic response

The term isotopic response refers to the occurrence of a new skin disorder at the site of another, unrelated, and already healed skin disease.[2] It was first defined by Wolf et al in 1985 and hence is also known as Wolf's isotopic response.[3],[4] The term "isoloci response" has also been suggested. The isomorphic response, first defined by Koebner, indicates the appearance of typical skin lesions of an existing dermatosis at sites of injurics.[2]

The differences and similarities between these two terms are obvious.[1],[2],[5] The isomorphic response describes the appearance of a skin lesion which is morphologically similar to an existing skin disease at the site of an injury of any kind. Thus the term "isomorphic" means "the same morphology" (as the existing disease). The term "isotopic response", on the other hand, describes the occurrence of a new, unrelated disease that appears at the same location as a previously already healed disease; hence "isotopic" means "at the same place".

= Koebner

(نفس المرض في نفس المكان الجرح)

(مرض جديد مكان مرض قديم ملتئم)

The localization of skin diseases remains one of the most elusive problems in dermatology.[2] The proposed etiologies of isotopic response are viral, immunologic, neural, vascular and locus minoris resistentiae (a site of lessened resistance). Most cases of isotopic response have been described in healed lesions (scars) of herpes zoster. The second disease has been reported to be granuloma annulare, Kaposi's sarcoma, leukemia cutis, metastasis, sarcoidosis, acne, lichen planus, granulomatous folliculitis, tinea, verrucae plana, molluscum contagiosum, squamous cell carcinoma, basal cell carcinoma, or multiple epidermoid cysts.[2],[3],[6],[7],[8],[9] A recent report describes herpes simplex appearing on a scrofuloderma scar.[4]

Ref.1- Lee HW, Lee DK, Rhee DY, Chang SE, Choi JH, Moon KC, et al. Erythema annulare centrifugum following herpes zoster infection: Wolf's isotopic response?. Br J Dermatol. Dec 2005;153(6):1241-3

2-Sharma RC, Sharma NL, Mahajan V, Sharma AK. Wolf's isotopic response: Herpes simplex appearing on scrofuloderma scar. Int J Dermatol 2003;42:664-6.

ERYTHEMA GYRATUM REPENS (Gammel's disease)

EGR

شبه دوايرالخشب و بتتحرك

Key features

- A figurate erythema that is migratory and composed of concentric rings with a wood-grain appearance
- It represents a paraneoplastic phenomenon and the most common underlying neoplasm is carcinoma of the lung
- The lesions may have associated pruritus and scale, and they characteristically exhibit rapid migration (up to 1 cm per day)
- The cutaneous lesions resolve when the neoplasm is successfully treated

or >40y.

def. Type of figurate Erythema ch- BY: (Migratory) Wood-grain like
Ass. underlying Cancer Lung.

HL · Et. & pathophysiology:

1. Cross Antigencity bet- skin / Tm
2. Tm → Alter cut. (Ag) → reacts
3. Tm Ags + Ab → deposit in skin

· EGR like lesions ± Seen in:
· BP, EBA, LAD, Annular T- Imbricula, PRP
· HP → Non specific.

· Epidemiology: Age → Adults > 40 (but ± 16-75; mean 63)
Sex → (M.) F = 2:1

· Clp:

EGR is Para Mg عند

· Cut. lesions
Multiple annular Erythematous lesions with chic Wood-grain or Zebra like appearance (Rings within rings) on Trunk & Extremities
The edge Covered with scale
should Rapid migration > EAC (upto 1cm/d)
May be pruritic
· Course: تكون

· Associations
1- Cancer (85%) usually (Lung) لازم
- Breast
- stomach
2- other cut. lesion:-
- Acq. Ichthyosis
- PPK
- Hypereosinophilia.

NB- lesions usually

ERYTHEMA MARGINATUM RHEUMATICUM

EMR

Rh fever ∈ child

Key features
▪ Migratory annular and polycyclic erythematous eruption
▪ Cutaneous manifestation of acute rheumatic fever
▪ Associated findings include carditis, migratory polyarthritis, Sydenham's chorea and subcutaneous nodules
▪ Seen more commonly in children than in adults

- **def:** Type of figurate Erythema occurs in the setting of active Rheumatic fever.
- **Etiology & Pathophysiology:**
  - Rheumatic fever is an abnormal Immunological response to a preceding infect∩ ∈ group A Beta → GABHs hemolytic streptococci & ch clinically by Triad of:
    - Fever
    - arthritis
    - Carditis.

    (FAC) → affect 3% of untreated pts. (5-15%)
    - <10% of R.fever show EMR
- **CIP:** Arciform & Annular or polycyclic ch By:
  - ⊙ Affect Trunk, Axillae & proximal Extrem.
  - ⊙ Migrat∩ rate ≃ 4–24 Cm/d
  - ⊙ Exacerbat∩ & remission over hrs-dys.

  → No specific Hp.

  → No ″ ″ (Self limiting & ↓↓ of R. fever has No effect on EMR)
- **NB:** other Cut. Manifs of R. fever:
  - SC Nodules (similar to Rh Nodules)
  - Urticarial like lesions.

ERYTHEMA MIGRANS
(Lyme disease, Lyme borreliosis, Afzeliu"s disease)

Key features

- Annular erythema develops at the site of the bite of a *Borrelia*-infected tick
- Several species of *Ixodes* ticks are infected with different genospecies of *Borrelia burgdorferi*
- Erythema migrans represents the initial cutaneous manifestation of disease and is seen in 60-90% of patients diagnosed with the disease
- Multiple secondary lesions that are smaller in size can occur as a result of spirochetemia or lymphatic spread

Lyme disease

- def. Multisystem infect- first presented with Cut. findings caused by Gram -Ve Spirochaetes Genus Borrelia & Transmitted by hard ticks genus Ixodes.

- Etiology: . Spirochaetes of genus Borrelia: (HL)
  - there are 11 species.
  - 3 of them causing Lyme dis. & collectively named Borrelia Burgdorferi sensu lato Complex:

B burgdorferi sensu Lato subspecies (HL)

subspecies	Geographic distribution	Associated disease
B burgdorferi sensu stricto	all North American and Europe	Classical lyme (But no Lymphocytoma)
B garinii,	exclusively in Europe	-Neuroborreliosis ← Lymphocytoma cutis.
B afzelii	Europe	-Acrodermatitis chronica atrophicans *(most common organism)* -Lymphocytoma cutis -/+ Morphea -/+ LSA ← Anetoderma

- Transmitted by the bite of Hard ticks species (HL)
  Ixodes - subspecies.
  - I. scapularix → North eastern & mid western US
  - I. pacificus → North western US.
  - I. ricinus → Europe.
  - I. ovatus → Asia

• Clp (has 3 stages as S)

• Age : Biomodal (children 5-14 & Adult: 30-50)

Stage	Manifestations
I-Early disease:	
1-localized (to site of inoculat:)	-Erythema Migrans (1-Y). -Regional lymphadenopathy LN - Mild constitutional manifs. (FAHM)
2-Disseminated (Bl. & lymphatics)	A-Cutaneous manifestations: -Disseminated Erythema Migrans -Lymphocytoma (Europe) (1%) B-Neurological: - Meningo-polyradiculoneuritis (Bann Warth Synd.) - Cranial neuritis -Bell's palsy C-Musculoskeletal: -Arthralgias, -Arthritis -Myositis D-Cardiac: -Pancarditis -Myopericarditis -Tachycardia -Atrioventricular block C-Lymphatic: -Regional or generalized lymphadenopathy D-Others: -conjuctivitis and iritis -hepatitis -non productive cough -microscopic hematuria or proteinuria
II-Late(chronic)disease:	A-Cutaneous manifestations: -Acrodermatitis chronica atrophicans B-Neurological: -Encephalopathy -Encephalomyelitis -Neuropathy C-Musculoskeletal: -Chronic arthritis

1- Erythema Migrans (لبيه الاسم ده أهم)

(Erythema Chronicum Migrans)

• incid: 60-90% of cases of Lyme dis.

• onset (Ip): 1-2 wks.

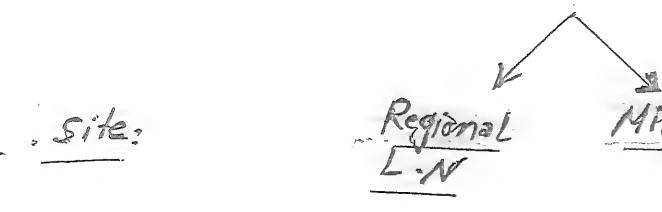
• durat: (if untreated): < 6 wks.

• Clp: The classical lesion starts as an asymptomatic Erythematous macule or papule that Expands peripherally over days-wks with diameter usually > 5 cm (CDC criteria) or average 16 cm (but ± upto 70 cm). often Central Punctum may be seen (bite). ; Lesion chBy:

1. Center of lesion in: North America: darker or of same color of periphery (Homogenous uniform lesion) / Same or darker

2 Periphery; raised, nonscaly, bluish red & warm

- ECM may be ass. with:-



- Site:

- In 25% of cases Multiple ECM lesions appear d.t either Multiple bites or dissemination

- Disseminated ECM differs from Tym in:-
  - Multiple
  - Smaller
  - less pronounced
  - appears ds. wks from onset of 1ry ECM..

SOME NBS (Emed. 2009)

1- Classic target lesion with concentric rings of erythema, which often show central clearing (annular configuration). Although this morphology was emphasized in earlier North American literature, it only represents approximately 40% of erythema migrans lesions in the United States. This pattern is more common in Europe. & because it has more chr. course ⟹ ECM (chronicum).

2- Location: Location of the bite is an important diagnostic clue. Ticks tend to feed in areas in which natural barriers prevent their forward progress, such as the popliteal fossa, groin, and axilla, or in areas in which elastic clothing or bra straps impede their journey. The thorax and trunk also are common spots. In children, the hairline and scalp are especially common locations.

3- Rashes very similar to erythema migrans have been reported in the southern United States from which *B burgdorferi* cannot be cultured. This disease is called southern tick-associated rash illness (STARI), or Master disease. As a group, distinctions can be made between classic erythema migrans and this illness, but significant overlaps exist such that the differences are not useful in diagnosing individual patients.

4 ⟹ ECM

- 50% having dissemination at Time of presentation
- If untreated
  - 60% Arthritis
  - 10% Neurological manif. (Sp. Bells palsy)
  - 5% → Cardiac involvement

5. High fever usually Not present in ECM & if it is present → Suspect
   - A- Alternative diagnosis
   - B- Additional tick born inf:
     - Babesiosis
     - Ehrlichiosis
     - Anaplasmosis.

6 Even though the lesion expands centrifugally, *B. burgdorferi* organisms have been found both in the center and the periphery of lesions of erythema migrans. The persistence of the spirochete in the skin for a long time after the tick bite may be due to an absence of the production of interferon-γ and an ineffective immune response[120]. Also, different immune responses to the various genospecies of the *B. burgdorferi* sensu lato complex (*B. burgdorferi* sensu stricto, *B. afzelii*, *B. garinii*) may lead to different clinical presentations[121] (e.g. borrelial lymphocytoma in Europe but not the US; see Ch. 74).

Histopathology

1- Routine → Non specific similar to deep Gyrate Eyth. ē Eosinophils & plasma cells in infiltrate.

2. Immunohistoch: - ↓ Les in dermis
- CD4, CD45 RO, Macrophages

3. silver stain → detect Borrelia.

as Warthin-Starry stain (ē ⊆ ⊗)

Borrelia Lymphocytoma

(Lymphocytoma Cutis = Lymphadenosis Benigna Cutis)

- Def, Histopath, ## → See pseudolymphoma.
- Same NBs: (1) Caused by Borrelia afzelii & garinii (So occurs in Europe & Not in USA)

also Borrelia Lymphomas are denified

(2) Site: . children → Ear lobule
. Adult → areola.
. less common on: Trunk, genitalia & extremities.

(3) present in (≃ 1%) of Lyme dis.

TOCR: only dis. that doesn't ✗ spont. ⊆ ⊆

Acrodermatitis Chronica Atrophicans [ADCA]

(Herxheimer disease)

- def. Cut manifestation of Late (chronic) European Lyme dis. usually caused by B. Afzelii (ass. i Long standing persistence in skin).
- Clp: - Usually occurs after (6 ms - 8 ys) from onset of inf. (but ± occur at same time) عكس نفس الوقت مع بداية
- More Commone in ♀ 40-70 ys.
- Itis a Biphasic disorder: (2 stages)

Early inflammatory stage "unilat"

Insidious onset of ACral Erythematous - violaceous Nodules & plaques ē Waxing & Waning Course for Years.

Late atrophic stage

- Thin
- Atrophic
- Translucent
- wrinkled
- ↓ Sweat, Sweaty Pap. Sebt

- Atrophy ē glistening "Cigg. Paper" appearance ē Prominent BVs.
- There may be: SC Nodules at forearm & Legs

Diagnosis of Lyme dis

1ry during different stages

A. during ↓ ECM :-

1. **Clinical diagnosis**: CDC accepted diagnosis for lesions > 5 cm but some cases show smaller lesions & so CDC defin. is for surveillance only (most cases have diameter ≥ 16 cm).
2. **Therapeutic diagnosis**: by giving Doxy or Amoxy & observe for improvement.
3. **Serological diagnosis**:
   - disadv. usually become +ve in 3-6 ws after inf. & the waiting for this period to confirm the diagnosis will → dissemination
   - Methodology: CDC instruct 2 steps.
     - 1st → ELISA or IF.
     - 2nd → WB (for +ve or +/- ELISA or IF)
       if detect IgM against 41 KDa flugellar Ag.

2008 · Newer assays detect ↓ of C6 peptide ↓ VsIE

4. Culture, HP & PCR (Non-specific)

B. During L. Cutis, Biopsy + chic site

C. Acrodermatitis chronica stage: serology is +ve

Treatment

1. Early localized → 2-3 ws
2. Mild Early dissim. or Mild late → 2 ws - 4 ws → Doxy 100 (1×2)/d or Amoxy 500 1×4
3. Severe " " or severe " → 2 - 4 ws [ceftriaxon 2gm I/V]

Annular erythema of infancy

def. EAC like-lesions That may affect infants.

AEt. as EAC but :

1- Dermatophytosis & Mg → Not Considered

2- Consider:
- LE
- Maternal Transplacental autoantibs
- Heavy intest. candidal colonizat°
- EBV.
- Pityrasporum inf.

Clp → EAC like

Path → EAC like but ē prominent Eosinophilic infilt. (Neutrophilic variant reported).

ttt → 1- ttt of underlying inf.
2- Na Cromoglycate
3- IFN-α

Eosinophilic Annular Eryth

Variant of Wells

Annular erythema associated with extractable nuclear antigens

def. EAC like lesions affecting patients with ANAs usually young adults.

Clp EAC like but differs in:

① photosensitive distribut° (specially face)

② Edge more broad > EAC.

AEt : ass. with ANAs:

1- NLE cases ē Anti Ro & U1RNP

2- SS & SLE → cases ē antiLa & U. RNA

Table 20.1 -- Differential diagnosis of figurate erythema.

DIFFERENTIAL DIAGNOSIS OF FIGURATE ERYTHEMA			
Disorders	Clinical features C/P	Histologic findings H/P	Cross references
1-Transient lesions (typically lasting <24 hours)			
Urticaria	Transient and recurrent wheals; pruritus	Superficial perivascular infiltrate of eosinophils and lymphocytes; occasional neutrophils	Ch. 19
Erythema marginatum	Polycyclic erythematous eruption; antecedent group A streptococcal infection; additional manifestations of acute rheumatic fever, e.g. arthritis and carditis	Scant perivascular infiltrate of neutrophils in the papillary dermis without vasculitis	See text
Erythema marginatum-like lesions of hereditary angioedema	Transient polycyclic erythematous eruption; favors trunk; precedes or accompanies episodes of angioedema	Minimal to no inflammatory infiltrate; dense perivascular and interstitial dermal deposits of bradykinin	Ch. 19
African trypanosomiasis	Annular erythematous patches on the trunk associated with fever spikes	Perivascular lymphocytic infiltrate; parasites are occasionally seen within the dermis	Ch. 82
Erythrokeratodermia variabilis	Transient gyrate or circinate erythematous patches (usually fade/migrate within a few hours); also fixed figurate hyperkeratotic plaques; *GJB4* mutations	Scant perivascular lymphocytic infiltrate; dilated capillaries	Ch. 56
2-Urticarial lesions lasting >24 hours			
Allergic urticarial eruption	Annular edematous plaques; favors trunk	Superficial and deep lymphocytic infiltrate with eosinophils	
Annular erythema of infancy	Recurrent annular erythematous plaques, usually lasting a few days; typically affects infants 3–11 months of age (see Fig. 20.5)	Perivascular lymphocytes and eosinophils	
Wells' syndrome	Edematous erythematous plaques, often annular or arcuate with a greenish color centrally; pruritus; peripheral blood eosinophilia	Diffuse infiltrate of eosinophils; flame figures	Ch. 26
Urticarial vasculitis	Urticarial plaques, often annular, that may have a purpuric component; pain, burning and/or pruritus; systemic manifestations in hypocomplementemic form	Leukocytoclastic vasculitis	Chs 19 & 25
Erythema migrans	Erythema slowly migrates from site of tick bite; influenza-like syndrome; secondary distant lesions	Superficial and deep perivascular lymphohistiocytic infiltrate; eosinophils and plasma cells in erythema migrans; mucin in LE tumidus and annular erythema of Sjögren's syndrome	See text and Ch. 73
Erythema annulare centrifugum (deep) EAC	Annular erythema with raised borders		See text
Lymphocytic infiltrate of Jessner	Annular erythematous plaques; favors face and upper trunk		Ch. 121
LE tumidus	Annular erythematous plaques; favors face, upper trunk > extensor forearms		Ch. 42
Annular erythema of Sjögren's syndrome[1] SS	Annular erythematous plaques; favors face, arms, upper trunk; most common in Asian patients; anti-Ro antibodies		Ch. 45
3-Granulomatous lesions			
Granuloma annulare GA	Skin-colored to pink annular and arcuate plaques with borders composed of multiple papules; favors acral and extensor sites	Palisading granulomas with altered collagen and mucin	Ch. 92
Annular elastolytic giant cell granuloma	Pink annular plaques with atrophy and hypopigmentation centrally; favors sites of chronic sun exposure	Granulomatous infiltrate with elastophagocytosis by giant cells (border of lesion); absence of elastic fibers (center of lesion)	Ch. 92
Interstitial granulomatous dermatitis (IGD); interstitial	Annular erythematous plaques (or, in IGD, linear cords); favors axillae, groin and	Palisading granulomas surrounding tiny foci of degenerated collagen;	Ch. 45

DIFFERENTIAL DIAGNOSIS OF FIGURATE ERYTHEMA			
Disorders	Clinical features	Histologic findings	Cross references
granulomatous drug reaction (IGDR)	lateral trunk; associated arthralgias/arthritis; IGDR is most often due to antihypertensive and lipid-lowering agents	neutrophils and eosinophils; little to no mucin	
Sarcoidosis	Red–brown annular plaques and papules; favors face; systemic manifestations	Sarcoidal granulomas ('naked tubercles')	Ch. 92
Borderline or tuberculoid leprosy	Annular plaques with raised erythematous borders and (in tuberculoid lesions) central hypopigmentation; asymmetric distribution; hypoesthesia, alopecia	Linear or oval perineural granulomas in the dermis; foamy macrophages and AFB in borderline lesions	Ch. 74
4-Papulosquamous lesions			
Erythema annulare centrifugum (superficial) EAc	Annular lesions with trailing scale; favors thighs, hips and trunk	Superficial perivascular lymphocytes with focal parakeratosis and spongiosis; focal hemorrhage in pityriasis rosea	See text
Erythema gyratum repens EGR	Concentric erythematous rings with wood-grain appearance; erythema moves □1 cm per day; associated with cancer		See text and Ch. 52
Pityriasis rosea P.R	Herald patch on trunk; oval annular papules and plaques with central fine scaling plus a collarette of trailing scale; Christmas-tree distribution on posterior trunk		Ch. 10
Tinea corporis T.C	Annular plaques with scale (exception: tinea incognito); pustules in border; concentric lesions in tinea imbricata; KOH-positive	Dermatophytes in the stratum corneum	Ch. 77
Lichen planus (LP) Lp	Violaceous annular plaques: gray–brown to brown hyperpigmentation centrally; mucosal involvement; photodistribution in actinic LP	Hypergranulosis, band-like lymphocytic infiltrate at dermal–epidermal junction, necrotic keratinocytes	Ch. 12
Annular LE (subacute > discoid), neonatal LE, mothers of boys with chronic granulomatous disease NLE	Photosensitivity; favors face (discoid), extensor upper extremities/upper trunk (SCLE), periorbital area (neonatal LE); anti-Ro antibodies (SCLE, neonatal LE)	Vacuolar interface dermatitis; often periadnexal lymphohistiocytic inflammation	Ch. 42
Seborrheic dermatitis SD	Erythematous annular plaques with scaling; favors face and central chest	Psoriasiform epidermal hyperplasia, spongiosis, perivascular lymphocytes	Ch. 14
Psoriasis PS	Annular scaly plaques with slow expansion	Parakeratosis, diminished granular layer, elongated rete ridges, neutrophils migrating into epidermis	Ch. 9
Ichthyosis linearis circumflexa of Netherton syndrome Ichth	Serpiginous or circinate erythematous plaques bordered by double-edged scale; trichorrhexis invaginata; atopic diathesis, elevated serum IgE	Psoriasiform features	Ch. 56
5-Lesions with absence or variable presence of scale			
Annular lichenoid dermatitis of youth	Red–brown annular patches or thin plaques with central hypopigmentation; favors groin and flanks; affects children and young adults	Lichenoid infiltrate; marked keratinocyte necrosis limited to the tips of rete ridges	
Secondary syphilis 2Hy	Annular plaques with central hyperpigmentation; favors face; flu-like symptoms; additional cutaneous manifestations; positive for RPR and FTA-ABS	Perivascular and interstitial infiltrate with plasma cells; also lichenoid or granulomatous infiltrate, exocytosis	Ch. 81
Mycosis fungoides MF	Annular erythematous or hypopigmented plaques, some with scale; admixed with classic lesions; often with pruritus	Infiltrate of atypical lymphocytes in the dermis and clustering in the epidermis; also plasma cells and eosinophils	Ch. 120

Erythema Multiforme (EM)

Key features

- A self-limited but potentially recurrent disease
- Abrupt onset of papular 'target' lesions, with the vast majority of lesions appearing within 24 hours
- Two types of target lesions are recognized: (1) typical, with at least three different zones; and (2) atypical papular, with only two different zones and/or a poorly defined border
- Target lesions favor acrofacial sites
- Has 2 types:
  1. Erythema Multiforme minor: typical and/or occasionally atypical papular target lesions with little or no mucosal involvement and no systemic symptoms
  2. Erythema Multiforme major: typical and/or occasionally atypical papular target lesions with severe mucosal involvement and systemic features
- A preceding HSV infection is the most common precipitating factor; occasionally, there are other preceding infections or, rarely, drug exposure
- Diagnosis of erythema Multiforme requires clinicopathologic correlation and is not based solely on histologic findings
- Erythema Multiforme does not carry the risk of progressing to toxic epidermal necrolysis

TEN TEN

NB:

Erythema multiforme is now regarded as probably distinct from Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

SJS TEN

Erythema Multiforme (EM)

def. Acute self-limited & sometimes recurring skin condition considered to be Type IV Hypersensitivity react° (or III) ass. with certain infections, medications & other various triggers.

Pathophysiology: EM is considered as Cut. Immune react° that's triggered by certain factors in genetically predisposed individuals:

A. Genetics: ↑ incid. of HLA-DQW3 in HAEM & HLA-B15,35 / HLA33 in recurrent EM

B. Triggers: → المحرك

PRECIPITATING FACTORS IN ERYTHEMA MULTIFORME		
Infections (approx. 90% of cases)	Viral	• Herpes simplex virus (HSV-1, HSV-2) (50%) HSV • Parapoxvirus (orf) • Vaccinia (smallpox vaccine) • Varicella zoster virus (chickenpox) • Adenovirus • Epstein-Barr virus • Cytomegalovirus • Hepatitis virus • Coxsackievirus • Parvovirus B19
	Bacterial	• Mycoplasma pneumoniae • Chlamydophila (formerly Chlamydia) psittaci (ornithosis) • Salmonella • Mycobacterium tuberculosis
	Fungal	• Histoplasma capsulatum • Dermatophytes
Drugs (<10% of cases)		Primarily: • Non-steroidal anti-inflammatory drugs (NSAIDs) • Sulfonamides • Antiepileptics • Antibiotics
Exposures		• Poison ivy
Systemic disease (rare)		• Inflammatory bowel disease (IBD) • Lupus erythematosus[1] (Rowell's syndrome) • Behçet's disease[1]
Idiopathic		

This is a nonexhaustive list based primarily on case reports and small series of cases. The most common causes are in bold.

· Pathophysiology: of EM ass:

1- HSV 2 Drugs (DAEM)

Mechanism of herpes associated EM (HAEM) → HL

Herpes simplex(HSV)-associated EM is a delayed type hypersensitivity (DTH) reaction that develops in response to infection in predisposed individuals. The process has been well studied and involves a number of steps:

1. HSV infection of keratinocytes, which may or may not result in signs of clinical infection.

2. CD34+ cells (Langerhans precursor cells) transport HSV DNA fragments to distant keratinocytes.

3. HSV gene fragments are expressed in these distant keratinocytes (HSV DNA and HSV-encoded proteins can be detected within the early red papules or the outer zone of target lesions in 80% of individuals with EM and may persist for 3 months after a lesion has healed MAY be due to difficulty clearing the virus from infected cells). However HSV virus cannot be cultured (low level of replication).

4. This is thought to be followed by an 'autoimmune' response (type 4) resulting from the recruitment of T cells (Th1) that respond to autoantigens released by lysed/apoptotic viral antigen-containing cells → IFN-γ → an inflammatory cascade resulting in the skin eruption of EM.

NB: Drug-induced EM involves a different mechanism with elevated tumour necrosis factor alpha rather than gamma-interferon and CD8+ cells and not CD4+ T helper cells.

· Epidemiology:

Age: any but usually: 20–40 ys
Sex: M ± > F
Race: No predilection

· Clp:

EM can be divided into:

Types of EM
1. Minor
2. Major
3. Persistent — CS, IBD, EBV, HSV
4. Continuous
5. Mucosal (Mycoplasma)
6. Recurrent (HSV)
7. Bullous
8. Urticarial

EM Minor	EM Major
· Cut lesions (Typical Target or papular Atypical Target)	· Cut lesions as Minor ± Bullae
· Absent or mild Mucosal affect	· Severe Mucosal affect
· (-Ve) prodromal (systemic) features	· Moderate prodroma (systemic features)
· Healing: 2-3 wks	· 2-6 wks
· MR : 0%	· <5%

1. Systemic prodroma
2. Cut
3. MM

(HSV inf. ↓ 3-14 days)

HSV inf. (Herpes Labialis in 50%)

↓ 3-14 days (ولكنه ممكن يحدث تحصل أثناء أو بعد ظهور EM)

1- Prodromal Symptoms (systemic manifs) →
- Absent in EM Minor & Mod. in EM major (50%):
- C/P: Non specific URT inf. (fever of low grade, Cough, Rhinitis & arthritis)
- durat°: ≃ 3 ds

↓ 3 ds

2 Cut. involvement ←

عدد كبير جدا

C/p: . Hundreds of skin lesions Erupt ē in 24 hrs & full involvement occurs over 72 hrs.

⊛ lesion start as: well defined pink macules → papules

غير الآخر → plaques of typical Target or Papular Atypical Target lesions.

Site: → Acrofacial: (صورة)
- Face & Neck
- dorsal hands & feet
- Elbows & knees (± ē grouping)

(U.L > L.L)

NB. Koebner phenomenon & photo accentuat° may occur
- lesions are ass. with Burning & pruritus
- distribution may be:
  - Linear
  - Zostriform
  - Blaschkoid

(dd 13)

↓ few days Later

MM involvement
- Absent or mild in EM minor & sever in Major EM
- Site: 1-2 mucosal sites are affected
- usually : oral MM but ± Eye, GIT, Genitalia.

Stomatitis / cheilitis → C/P: Mucosal redness & swelling → Blisters → large, shallow, painful ulcers

Typical → Lips: swollen ē Hgic crust
↓
difficult speaking & swallowing

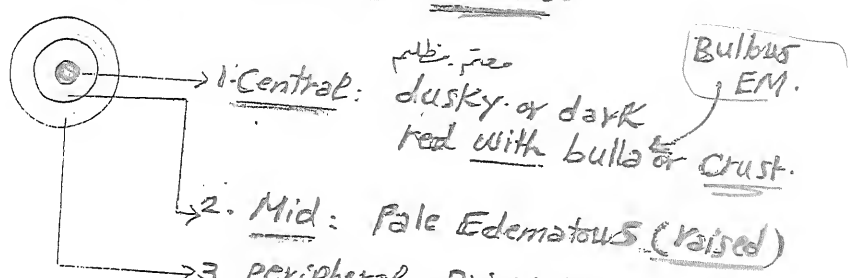
Types of Target lesions

Typical Target (Iris lesion)

Well defined

def: rounded, regular, ≤3 cm diameter

Pathology → Palpable with 3 Zones:



Atypical Target (Targetoid)

def: as Target but formed of 2 Zones & /or poorly defined border.

- Papular Atypical Target → acute → EM
- Macular (flat) Atypical Target → acute → SJS/TEN

Course:

1. Resolution of EM occurs:
   - EM Minor → 2–3 wks
   - EM Major → upto 6 wks

   Without scarring but (±) ē dyspigmentation

2. Complications (Mucosal)
   - usually (No) Complication except → 2ry bact. Inf. / Immuno Compromised
   - More ē EM Major; Includes: EM Major.

   (1) Ocular: conjuctivitis, Iritis, Uveitis, Symblepharon & ± Blindness.

   (2) oral: difficulty in consuming food → Dehydration

   (3) Genital: (Vaginal & Urethral lesions are rare):
   retention, phimosis, Hematocolpus, Urethral stricture.

MR
- EM minor → 0%
- EM Major → < 5%

Ref.

Fever & Bullae → Histopathology

EM is 1 Prototype of Vacuolar form of ID.

Dermis

VID with individual KCs (Basal) Necrosis (Satellite KCs). or Apoptosis ass. with Superficial dermal Edema & sparse-moderate perivascular Lymphoid (CD4>CD8) infiltrate.

Epid

- others:
  - Epidermal spongiosis & Exocytosis.
  - Satellite KC Necrosis (intra epid. Lymphocytes attached to Necrotic KCs)

IgM, C3 → Immunofluorescence: → Non Specific
1. granular IgM & C3 around BVs & focally at DEJ
2. HSV Ags are +Ve within KCs by PCR
3. HSV genomic DNA can be detected by PCR.

→ NB: on pathology:
1- EM is clinicopathological diagnosis; Not a pure pathologic diagnosis → Histopath. is chic but not specific
+ required to exclude other conditions
2- diff. bet. Drug induced EM & HSV induced:

TNF-α, CD8 → Drug induced (DAEM)
- More KC Necrosis
- More Pigment incontinence.

IFN-γ, CD4 → HSV induced: (HAEM)
- More Exocytosis & VID
- More upper papillary dermal Edema.
- Nuclear dust in papillary dermis.
- CD4 > CD8

Eosinophils

Acrosyringeal Concentration of Apoptotic KCs (clue for DD)

3- CD8 > CD4.
diseases of Necrotic (Apoptotic) KCs:
- FDE
- FL
- GVHD
- CTDs
- Viral Exanthema
- Phototoxic dermatitis.

- DD of EM: (causes of Targetoid lesions):
  1. SJS/TEN
  - Urticaria
  - FDE ← Fixed Drug Eruption.
  - Vasculitis (e.g AHEI) Acute hemorrhagic edema of infancy
- PND → Paraneoplastic Pemphigus
- EAC → Erythema Annulare Centrifugum
- SCLE → Subacute Cutaneous LE

- Diff. bet EM & Urticaria :-

Table 21.3 -- Differences between urticaria and erythema multiforme.

DIFFERENCES BETWEEN URTICARIA AND EM	
Urticaria	EM
Central zone is normal skin	Central zone is damaged skin (dusky, bullous or crusted)
Lesions are transient, lasting less than 24 hours	Lesions 'fixed' for at least 7 days
New lesions appear daily	All lesions appear within first 72 hours
Associated with swelling of face, hands or feet (angioedema)	No edema X

- Diff. bet. EM & Generalized FDE:

There is clinical & Histopath. overlap.

: علشان نفرق *

عدد العدد No of lesions at first outbreak

- in FDE → fewer ✓ قليل
- in EM → Hundreds ✓ كتير

Treatment of EM

Prophylactic ttt (For recurrent EM)

Inf. / Drugs

1- remove the drug

2- Mycoplasma pneum. → Erythromycin

3- HSV → chr. suppressive for recurrent HAEM > 6 /y.

- dose: ACV: 10 mg/kg/d in divided doses (200-400 TwiCal d)
- durat°: (6-12 ms)

↓ if failed

- VCV → 0.5-1 gm/d
- FCV → 250 mg/d

Recurrent

- وظيفة: ان حتى المرضى اللي بيجيلهم EM بدون HSV نعطي لهم ACV لان العدوى ممكن تكون sub clinical inf. أو نعمل HSV erology

↓ if failed (Idiopathic EM)

- Continous use of:
  - Dapsone
  - Antimalarial
  - Azathioprin
  - Thalidomide
  - CyA
  - PUVA

Active ttt (Acute rash)

Symptomatic ttt

1- Itching → oral antihistamines & Topical Cs

2- oral pain → mouth washes containing anaesthetics & Antiseptics

3- Eye → ophthalmologist.

For:
- EM minor (تعالج بالبيت)
- Severe EM Major → Hospitalizat°.

4- هل نعطي Cs؟ وكم؟؟

- its use is controversy (as it ± ↑ risk of infectious complications)

يبين لو هانعطيها يبقى بشرطين:

1. Early initiat°
2. Severe dis

give prednisolone or pulse MP.

STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS (SJS/TEN)

Key features

- Prodrome of upper respiratory tract symptoms, fever and painful skin
- Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two rare, potentially fatal adverse cutaneous drug reactions of differing severity, characterized by mucocutaneous tenderness and erythema as well as extensive exfoliation
- SJS is characterized by <10% body surface area of epidermal detachment, SJ SJS –TEN overlap by 10-30%, and TEN by >30%
- The medications most frequently incriminated are antibiotics, non-steroidal anti-inflammatory drugs, and antiepileptics. TEN and SJS usually occur 7-21 days after initiation of the responsible drug
- The average mortality rate is 1-5% for SJS and 25-35% for TEN; it can be even higher in elderly patients and in those TEN patients with a very large surface area of epidermal detachment
- Exfoliation is due to extensive death of keratinocytes via apoptosis; the latter is mediated by interaction of the death receptor–ligand pair Fas–FasL
- Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the causative drug(s), and rapid initiation of supportive care and specific therapy
- Specific therapies that have the potential to selectively block keratinocyte apoptosis, such as high-dose IVIg, may provide added benefit over supportive care alone

سؤال امتحان

Stevens Johnson Syndrome & Toxic Epidermal Necrolysis

(SJS/TEN)

def. SJS/TEN is a very rare, acute serious & potentially fatal skin reaction in which there is (sheet-like) skin & mucosal loss usually caused by Medications.

Cause: usually **Drug induced:**

- ① > 200 drugs can cause SJS/TEN (so any drug can cause SJS/TEN unpredictably).
- ② **Risky drugs:**
  - Drugs with Longer half lives
  - **Most Common drugs:**
    - Sulfonamides (Septrin®)
    - Allopurinol
    - NSAIDs (oxicam Type)
    - Anticonvulsants.
- ③ **Risky Patients:**
  - **HIV** why?? ↑use of sulfonamides; abnl pattern of production or detoxification of drug Metabolites
  - GVHD
  - CTDs

1st: A- 1st exposure:
- Antibiotics → 1-3 wks (2 wks)
- anti Convulsants upto 2m.

B- Previous Exposure (TEN): 2ds.

Drugs that most commonly cause SJS/TEN

Antibiotics Antifungals Antivirals	• Sulfonamides, e.g., cotrimoxisole; beta-lactams i.e., penicillins, cephalosporins • Imidazole antifungals • Nevirapine (non-nucleoside reverse-transcriptase inhibitor)
Allopurinol	
Nonsteroidal anti-inflammatory drugs (NSAID) (oxicam type mainly)	• Naproxen • Ibuprofen
Anti-convulsants	• Carbamazepine • Phenytoin • Phenobarbital • valporic acid. • Lamotrigine.

Pathophysiology → unknown but 2 Mechanisms were proposed:

1- Genetic Mechanism:

A. Patients ē SJS/TEN & Their 1st degree relatives may have genetic defects that → accomulat~ of Toxic Metabolites of The drugs.

For example: Patients ē Sulfonamide induced TEN have been shown To have "Slow acetylator GenoType" → ↑ products of sulfonamide hydroxyl amine (Via P450 Path way) W is a Toxic Metabolite that → TEN

← Via either: ① Direct toxic effects or
② Hapten Mediated Mechanism → break Self Tolerance to Endogenous proteins.

↓

Perforin Mediated KCs apoptosis

B. ↑ in Cid. of HLAB12:

. in Allopurinol induced TEN → HLA B5801
. in Carbamazepine " " → HLA B1502

2- Interaction bet. Cell surface death receptors:-

(Fas-fasL Mechanism): The interaction bet Fas & Fas-Legand → apoptosis. this interaction can be blocked by IVIG → stop of dis. progression ē in 1-2 ds ē No mortality.

What is Perforin??

making mono-me granules re- from NK cells → The Target y forming Po- rs & Tubular st- ures (not unlike attack Complex plement n.

HL

Stimuli of apoptosis

1. Cellular stress.
2. Growth factor withdrawal
3. DNA damage
4. Cytokines release (TNF)

↑ FasL Expression by KCs & localized Extracellularly

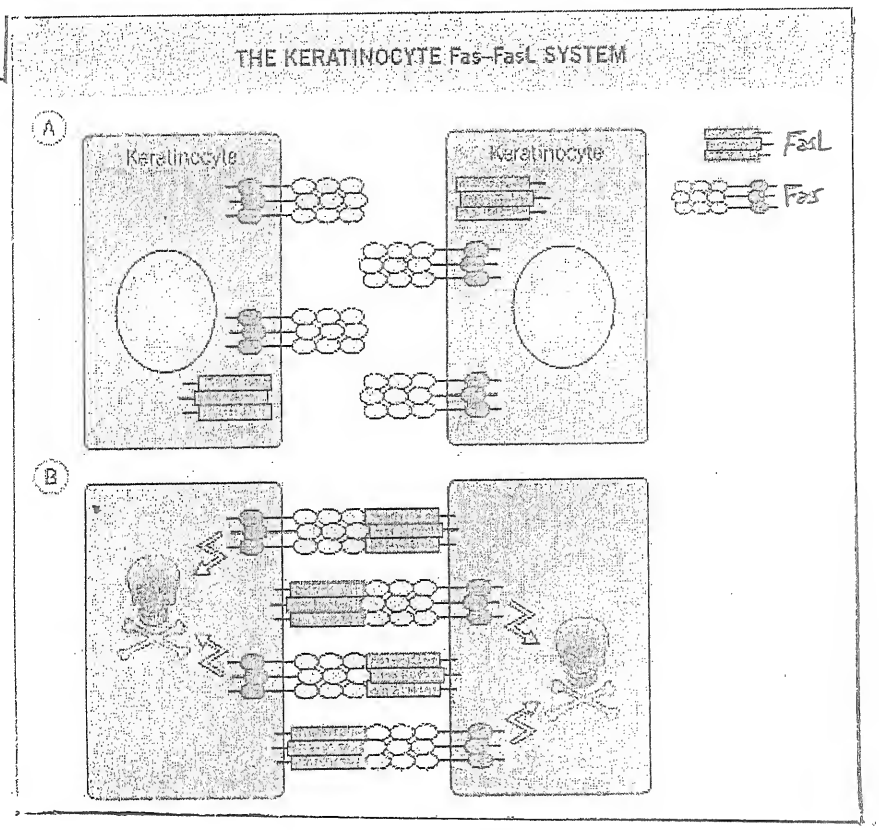


Fig. 21.5 The keratinocyte Fas–FasL system in normal skin and its role in toxic epidermal necrolysis (TEN) and treatment with IVIg. A In normal skin, low levels of Fas ligand (FasL) are expressed by keratinocytes and localized intracellularly. B In lesional skin of TEN, high levels of FasL are expressed by keratinocytes and localized on the cell surface. Upon contact with Fas, cell surface FasL induces Fas multimerization and rapid signaling leading to keratinocyte cell death by apoptosis.

Initiation of Fas Signaling Pathway of Apoptosis.

Fig. 21.4 The Fas signaling pathway of apoptotic cell death. The death receptor Fas and its ligand FasL are transmembrane proteins. Fas signaling is triggered in the target cells by receptor tri(multi)-merization, induced upon contact with membrane-bound FasL from an adjacent cell. Subsequently, recruitment of intracellular signaling proteins FADD and pro-caspase-8 leads to activation of the protease caspase-8 as well as apoptosis due to subsequent activation of downstream effector caspases (caspases-3, -6, -7), which cause cellular disintegration and death. Stimuli that induce apoptosis include cellular stress, growth factor withdrawal, DNA damage and cytokines.

· Epidemiology:

- Age: any but common in 46 – 63 (d.t ↑ drug intake)
- sex: M:(F) = 1:1.5.
- race: any

· C/P:

1- Drug Exposure: → after period differs acc. to 1st or prev. Exposure (See below) →

2- Prodromal Symptoms for 1–3 ds → · c/p: Flue like or URTI like:
- Fever (High & persistent).
- Cough
- Sore throat
- dysphagia
- runny nose
- Sore Eyes
- General aches.
- ± Hepatitis, Cytopenias.

· onset of TEN after drug intake:
- 1- 1st Exposure of drug:
  - in Sulfa antib. → 2 wks
  - in anticonv. → upto 2 ms
- 2- previous Exposure that caused TEN: 2 ds.

↓

3. Mucosal Involvement ←
- occurs in > 90% of cases.
- onset: Early before skin or during prodrome.
- sites of C/P: at least (2) mucosal sites are involved:
  - Eyes: → Conjunctivitis
  - Mouth: → cheilitis & stomatitis
  - Oesoph. → dysphagia
  - URT → Cough & RD ← URT
  - Genital & Urinary → ulcers
  - GIT → diarrhoea. ← GIT
- They are very tender

↓

4. Skin involvement

↓

2 Types of skin Lesions:

· Early (3) +B1
- usually: Macules: Erythematous, dusky red or purpuric
- or · May be: · Targetoid (flat atypical target)
  · Scarlatiniform
- These lesions ch. by:
  - ⊙ Very Tender & painful
  - ⊙ show (+ve) pseudo-Nikelsky sign

→ hrs – ds →

· Late:
- Large flaccid fluid filled blisters → Epid. detatchment with exposure of underlying dermis which is raw & Bleeding ((scalded))
- · (+ve) Asboe Hansen sign.

· Epid → wet cigarette paper
· Dermis → scalded

Sites of skin involvement:

- Start on the Trunk & extends rapidly to face & Limbs (sp. photosensitive & Trauma sites).
- distal legs & arms: relatively spared but Palmo-plantar areas may be an early sites of involvement (bullae will be Tense ??)

↓

After diagnosis of SJS/TEN clinically you have to do 2:

A Classification of the patient: based on extent of skin detatchment.

Note: detatched = detachable (By Nikolsky)

SJS	SJS/TEN overlap	TEN
<10% of BSA	10-30% of BSA	>30% of BSA
MR: 10%		MR: 30%

B Asses Severity & predict the out come by: SCORTEN

BSA → Body surface Area

Table 21.6 -- Scorten.

SCORTEN	
Prognostic factors (7)	Points
Age >40 years	1
Heart rate >120 bpm	1
Cancer or hematologic malignancy	1
BSA involved on day 1 above 10%	1
Serum urea level (>10 mmol/l)	1
Serum bicarbonate level (<20 mmol/l)	1
Serum glucose level (>14 mmol/l)	1
SCORTEN	Mortality rate (%)
0-1 → 3	3.2
2 → 15	12.1
3 → 30	35.8
4 → 60	58.3
=5 → 90	90

ارقام تقريبية

NB Healing occurs ē epithelialization from NL surrounding skin & Form H. follicles (No need for Graft).

Complications of SJS/TEN

Toxic Epidermal Necrolysis

This condition can be fatal due to complications in the acute phase. The mortality rate is up to 10% for SJS and at least 30% for TEN.

A-During the acute phase, potentially fatal complications include:

- Dehydration
- Malnutrition
- Infection → skin, MM → Pneumonia, Blood → Septicemia
- DIC & MoF

B-Longterm complications include:

1. Skin: Dyspigm. & Scarring (at pressure areas & dt Inf.)
2. Nails: pterygium & dystrophy.
3. Joint: Contractures.
4. Genitalia:
   - phimosis.
   - Vaginal Synichiae.
   - ulcers
5. Eye:
   - Conjunctivits
   - Keratitis → opacities & ulcers.
   - Symblepharon → adhesion bet Eye lid & Eye ball
   - Ectropion or Entropion.
   - Trichiasis → Inverted Eye lashes.
   - Synichiae → bet. Iris & Cornea.

6. Cause of death
   1. Inf (esp staph & pseudemon.)
   2. fluid loss & Elect. imbalance
   3. Insulin loss or ↓ response.
   4. Hypercatabolism.

Invs. of SJS/TEN

1 Lab:
- ① CBC
- ② Chemistry profile
- ③ LFTs
- ④ RFTs
- ⑤ PT
- APTT
- ⑥ Culture of Blood & denuded areas.

2 Rad:
1. Baseline radiograph: d.t frequent Trachiobronchial involvement & RD
2. GIT: radiograph to detect affect^

3 Histopathology: → confirm Dx / Exclude other dis: SSSS, AGEP

Early Lesions

- KC Necrosis (scattered (individual) Apoptotic KCs in basal & suprabasal Layers)

↓

This correlates with the dusky to gray color of lesions

واللى أول ما نشوفها هلاحظ نعرف ان الحرقين هايدخل ع :

Full-blown Epid Necrolysis.

Late Lesions

↓

subepid. Blisters with overlying confluent
① Necrosis of entire Epid. + sparse
② Perivascular Lymphocytic infilt of papillary dermis.

كل ال epid — Full thick. Epid. Necrolysis.

Note

Lymphocytes of:
- Epid.: CD8+ & Macrophage
- Dermis: CD4+.

CD8+ / CD4

Blister at granular Layer
· Neutrophilic infilt.
· Epid. pustules

DD of SJS/TEN

- EM
- SSSS
- AGEP ← (الأهم)
- Generalized FDE → Fixed drug eruption
- other:
  - PNP → Paraneoplastic Pemphigus
  - LAD
  - LE → Lupus E
  - Kawasaki
  - Acute GVHD Host versus Host dse

---

1. EM: → .Typical Target lesions
   .. affect Face & Extremities
   ↓ See table

هي الحالة اللي فيها Targeted lesions

. Also so table of diff. of EM.

2. SSSS:

. Etiology → staph. aureus Exotoxin (Epidermolysin) → attack DSG1

. Age: → .usually (Newborn) & (Young Children)

. adults may be affected if: RF or Immunosuppressed.

→ (No) MM or pp affection.

- Nikolsky sign is (+Ve) & Fragile bullae are (+Ve) but They lead to: (Exfoliat^n) ̄c leaving Bed of intact epidermis (instead of scalded Dermis of TEN). d.t difference in level of separat^n. ??

- Nasal discharge → frequently present
- Histopath. → see before.

3 AGEP:

def. Adverse cut. Drug reaction ch by Large areas of erythemas studied ē small (<3mm) "non" follicular Pustules. MM → (20%) & Nikolsky sign (± Ve)

← clinically → Neutrophilia, Eosinophilia, pustules — all are (against) TEN

4. Generalized FDE:

- Multiple Mucocut. affect^n may occur.
- overlap clinically & Histologically may occur ē SJS.
- determinat^n of No of lesions during 1st out break may be useful (Fewer) (22 ساب لبطا)

5- Others: ... سريعا

- PNP, LABD, GVHD → clinical & Path. criteria (ē +Ve IF).

Note: Vancomycin → Commonest drug Causing LABD ... uncommon cause of TEN.

Kawaski:
- No conj. Exudate
- PP & perianal → epid split
- No Targetoid lesions.

TEN like Vesiculobullous lesions seen in Patient ē SCLE & SLE may occur & called

« Acute synd. of apoptotic x pan-Epidermolysis »

((ASAP synd.))

(Acute Synd of Apoptotic Pan epidermolysis)

Treatment of SJS/TEN → IVIG + Supportive

(Hospitalization)

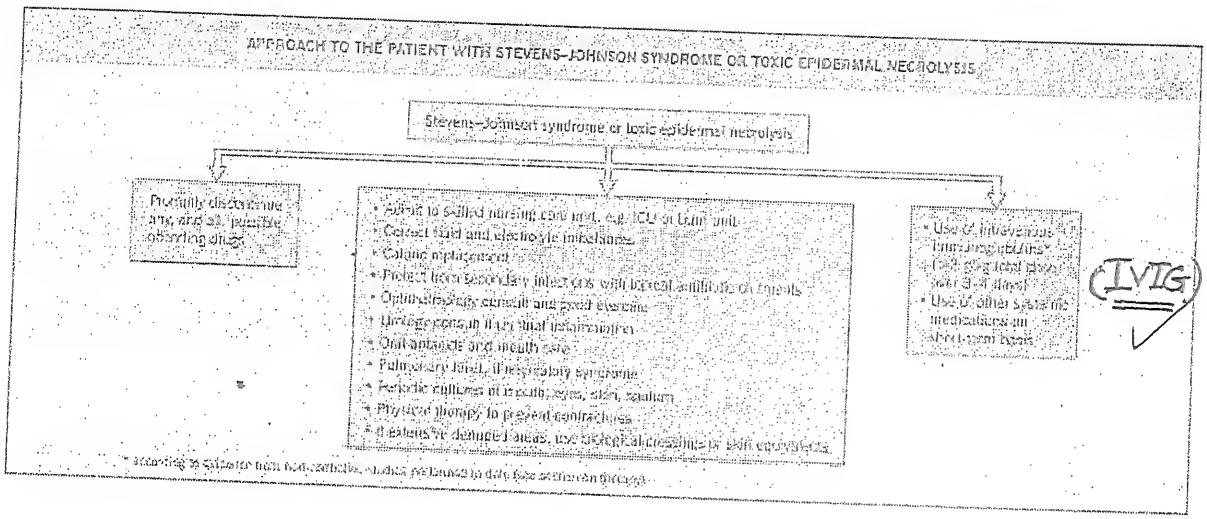


Fig. 21.13 Approach to the patient with Stevens–Johnson syndrome or toxic epidermal necrolysis.

العناية وأعلاه
1. ICU or burn unit.
2. Correct Fluid & Electro Imbalance
3. Calloric intake
4. Topical Antib.
5. Mouth Care
6. Eye Care (بتابع رمد)
7. Urological Care (بتابع مسالك)
8. Joint Care (بتابع طبيعي)

IVIG → حتى يوجد Cyclosporine أو أفضل حاجة

- NB. Role of CS: Controversy but may be used in short courses (Pulses)
- X Thalidomide: avoided (↑MR)
- Cyclosporine: 3-4 mg/kg/d
- Cyclophosphamide: 100-300 mg/d
- N-acetyl Cysteine: 2g/6hrs
- IVIg → 1 gm/kg/d for 3 Consecutive days

Avoid ... thalidomide

3 Consecutive days

Diff. bet: SJS / TEN

	EM	SJS/TEN
Cause Age Sex	- Inf. (HSV) - 20-40 Ys - M > F	- Drugs. - > 46 Y - F > M
prodrome	Absent - moderate	Severe ✓
Skin: A. site: B. lesion: C. BSA	Acrofacial 1. plaques, Target or papular atypical Target. 2. ± Bullae (EM Major) 3. No epid. detachment < 10%	Trunk then extends → Face, Neck. Macules, Flat atypical Target Bullae Epid. detachment > 10%
MM: - onset - No - severity Int. organs affect	Skin بعد أو مع Common but mild - Mod. usually only oral (1 Mucosal site) absent. ✗	Skin قبل أو مع Severe, involving at least 2 Mucosal sites (2-3). Not frequent
Durat Complications: MR	2-6 ws, No ✗ 0% - < 5%	> 2-6 ws. ± Complicated (أذى) 10-30% ↑
Pathology	VID with individual KC Necrosis & stellites + sparse-mod. papillary dermal Lymphoid infilt ē Edema. CD4 > CD8	Subepid. Blisters ē Full thickness Epid Necrosis & Sparser Lymphoid infilt. CD8 > CD4
Tt	See EM → Prophylactic ACV; active Sympt + CS	See SJS/TEN. IVIG

Target
± Bullae
No detachm

Intravenous mmunoglobulin

- **Definition:** Intravenous immunoglobulin (IVIG) is a sterile solution of globulins extracted from the pooled plasma of about 10,000 to 20.000 individuals.

- Mechanism :-

  1. Immunosuppressive: (-- Complement Mediated damage & block Fc Rs on surface of Macrophage & B-Cells)
  2. Anti-inflammatory: ↓ inflammatory Mediators
  3. Antimicrobial: ↓ circulating pathogens.

  4. Its recent success in treating TEN is believed to be a function of its ability to inhibit apoptosis. Theoretically, IVIG acts as a Fas (CD95)-blocking antibody, inhibiting Fas: Fas ligand-induced keratinocyte death.

  5. *NB- In persons with Kawasaki disease and dermatomyositis, IVIG is thought to inhibit the generation of membrane attack complexes (C5b-C9) and subsequent complement-mediated tissue damage by binding the activated components C3b and C4b, thus preventing their deposition on target surfaces.*

Indications:

A. FDA approved indications: *7 conditions:*

1. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
2. Immune Thrombocytopaenic Purpura (ITP)
3. Primary immunodeficiency states eg. *Iry and X-linked agammaglobulinaemia.*
4. Chronic Lymphocytic Leukaemia
- Paediatric type-1 HIV
- Kawasaki syndrome
- Prevention of Graft vs. Host disease in adult bone marrow transplant recipient

(The first four conditions account for 70% of IVIG use)

B. Non FDA approved indications *(offlabel uses):* → see table :

Dosage & Administration:

الطريقة للإعطاء: 1-2 gm/kg . In 500-1500 ml saline or glucose (IV) infusion over (2 hrs) for 2-4 ds. every 4 wks (4 weekly)

High doses → in inflamm & autoim. dis.

then tapered to every 2-4 ms.

NB: in Kawasaki dis: single (2 gm/kg) over 12 hs → effective.

How long do the effects of IVIG last?

The duration of the response from IVIG depends on the individual's metabolism and the disease state. On average, the effects of IVIG can last up to a month after each administration.

Contraindications:

1-Absolute: (3)
- History of hypersensitivity to IVIG. (IV IG)
- // // // to Thimerosal (Thimerosal)
- IgA deficiency *(Deficiency of IgA occurs in about 1 in 700 of the population and should be screened before IVIG therapy is instituted)* (IgA)

2-Relative:
- RF & HF (↑ Risk of fluid overload)
- RA & Cryoglobul (↑ Risk of RF)
- pregnancy (C)

Comprehensive Dermat →

Side effects: IVIG is generally well tolerated. Most side effects are mild and self-limited.

A-Common side effects (within 30-60mins) → "Vasomotor"

- Flushing.
- Urticaria
- Headache
- Chills
- Fever — FAHM
- Nausea or vomiting
- Wheezing
- Lower back pain
- Tachycardia (rapid heart beat) — HR
- Changes in blood pressure — Bp

- Myalgia (muscle pain)

These symptoms can be managed by stopping the infusion or a patient can be premedicated with antihistamines and intravenous hydrocortisone.

B-Rare side effects:

- Acute renal failure *(most common after use of sucrose-containing products which can cause an 'osmotic nephrosis'.)*
- Blood clots.
- Haemolysis.
- Neutropaenia.
- **skin reactions:**
  1. Blistering eczema is the most common (a type of dermatitis). It often begins at about 8 to 10 days after exposure to IVIG. The rash characteristically begins as a dyshidrotic eczema (pompholyx) but this may be followed by a more generalised eczematous eruption that spreads throughout the body. The affected individual may become erythrodermic (red all over) and pruritic (itchy).
  2. Urticaria
  3. Maculopapular rash.
  4. Lichenoid eruption (like lichen planus)
  5. Diffuse hair loss.
  6. Cutaneous vasculitis.

Drug interact: No interact but may ↓ its efficacy. the live attenuated Vaccines (LAV)

disadvantage: Cost, ≃ 30,000 LE / cycle

3: 1. Risk of infection from IVIG: The pool of donors is carefully screened to eliminate anyone with abnormal liver function or exposure to viral hepatitis or HIV infection. The process of obtaining IVIG itself removes viruses and bacteria from the plasma. Therefore, IVIG should not pose any risk of hepatitis C, hepatitis B or HIV transmission. Since the introduction of newer techniques of obtaining IVIG in 1987, there have been no cases of transmission of these viruses.

2. What happens upon re-exposure to IVIG?: When an individual develops a skin reaction to IVIG, a second exposure may cause the rash to appear earlier (generally around 8-10 days after infusion) and become more extensive. This is because the immune system has developed memory T-cells and subsequent responses are faster and more severe. Switching the type of IVIG may cause a less severe reaction.

الاسماء التجارية:

- Gammagard S/D (Baxter/Hyland; Deerfield, Ill)
- Gammar-IV (Armour; Blue Bell, Pa)
- Gamimune-N (Miles; Elkhart, Ind; Bayer)
- Iveegam (Immuno-US; Rochester, NY)
- Polygam S/D (Baxter/Hyland for American Red Cross; Washington, DC)
- Sandoglobulin (Sandoz; Vienna, Austria)
- Venoglobulin-I or Venoglobulin-S (Alpha Therapeutic; Los Angeles, Calif)
- Carimune/Panglobulin (ZLB Bioplasma/ARC Swiss Red C...

- Emed.
- Katzung
- ONNZ
- Rook

FLUSHING سؤال امتحان

Introduction:

Flushing is the term used to describe transient and episodic reddening of the skin, most commonly of the face, and less often the neck, ears and upper chest.

Table 10b-2 -- Causes of flushing.

CAUSES OF FLUSHING

1- **Physiological:** *as part of normal thermoregulation in response to :*
- *Exercise
- *Hot drinks
- *Hot environment
- *Blushing (emotionally triggered..حمرة الخجل)

2- **Exogenous agents:**

- *Alcohol* الخمر
- *Drugs*
  - * Angiotensin-converting enzyme (ACE) inhibitors ACEI
  - * Calcium channel blockers CCBs
  - * Calcitonin
  - * Chlorpropamide[*1]
  - * Cholinergic agonists (e.g. pilocarpine)
  - * Cyclosporine
  - * Disulfiram[*1]
  - * Fumaric acid esters (ttt of PS.→ttt by trental as it –TNFα)
  - * Gold ('nitritoid reactions')
  - * Hydralazine
  - * Nicotinic acid ← smoking ← الله يهين
  - * Nitrates (e.g. glyceryl trinitrate)
  - * Opiates
  - * Prostaglandins (PGs)
  - * Sildenafil, tadalafil, vardenafil Viagra
  - * Tamoxifen
- *Foods*
  - Spoiled scombroid fish(التونا والماكاريل الفاسد) →flush,sweating,vomiting,diarrhoea due to histamines (لو عاوز تشخصه قيس هيستامين البول)
    ttt→H1,2bloekers,Cs,Epinephrin.
  - Spiey food (gustatory flushing, ass. with sweating).
- *Foods additives*
  - Monosodium glutamate (MSG), sodium nitrite, sulfites

3- Menopause (80% of menopausals). [Hot Flushes] متحان

4- Neurologic disorders :

NB Acral Flushing
- Erythema Ab Igne
- Erythromelalgia
- Post Raynauds

1 Acral flushing

CAUSES OF FLUSHING

- Anxiety
- Autonomic dysfunction
- Tumors (e.g. hypogonadal pituitary tumors)
- Migraine
- Frey's syndrome (auriculotemporal syndrome)
- 5- Systemic diseases
  - Carcinoid syndrome → Ø: Urine 5 H I. Acetat (Serotenin Metabolite)
  - Mastocytosis
  - Pheochromocytoma → Ø Urine: Vanillylmandelic acid
  - Medullary carcinoma of the thyroid } 2 Thyroid
  - Thyrotoxicosis
  - POEMS syndrome
  - Pancreatic tumors (e.g. VIPomas)
  - Prostaglandin-secreting renal cell carcinoma

6- Cut: Rosacea. 7- Idiopathic.

Pathogenesis:

Flushing is caused by relaxation of dermal BVs ⓦ. may be Mediated by either:

1. Autonomic Nervous system → Flushing + sweating (Wet Flush)
2. Vasoactive Mediators: → Flushing (without) sweating (Dry Flush).

Table 44.2 Causes of flushing. (Mediators of VS relaxation).

Cause	Proposed mediator(s)
Physiological	Autonomic
Menopausal	Autonomic
Drug induced	Various
Alcohol	Acetaldehyde
Chlorpropamide and alcohol	Acetaldehyde
Food	Autonomic
Scombroid fish poisoning	Histamine
Carcinoid syndrome	Serotonin, Prostaglandins, Bradykinin, Histamine
Mastocytosis	Histamine
Thyrotoxicosis	Thyroxine
Medullary carcinoma of the thyroid	Prostaglandins, Calcitonin
Pancreatic tumours	Vasoactive intestinal peptide (VIP)
Insulinoma	?

Complications:

1. Blushing → anxiety & embarrassment
2. Fixed Erythema, Telangiect & Rosacea.

DD 1- Burning sensation + Erythema AICDs, photodamage, photosensitivity.

2 Rosacea ??

1. Remove underlying Et (Tm Menopause (SST); anxiety → anxiolytic)
2. Idiopathic → clonidin, BB
3. Menopausal → clonidin, SSRIS, ERT
4. Blushing → Psychotherapy, Anxiolytic, clonidin
5. resistant Cases → surgical

Paroxetine

NB Paroxetine is FDA for Menopausal Flushing